FORMULATION DEVELOPMENT AND *INVITRO* EVALUATION OF MOUTH DISSOLVING TABLETS OF LERCANIDIPINE HYDROCHLORIDE BY DIRECT COMPRESSION METHOD: AN APROACH TO IMPROVING ORAL BIOAVAILIBILITY

A Dissertation submitted to

THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY,

CHENNAI- 600 032

In partial fulfilment of the award of the degree of

MASTER OF PHARMACY

IN

Branch-I -- PHARMACEUTICS

Submitted by

Name: RAJESH. R

REG.No.261610257

Under the Guidance of

Mr. C. KANNAN, M.Pharm.,

DEPARTMENT OF PHARMACEUTICS

J.K.K. NATTARAJA COLLEGE OF PHARMACY

KUMARAPALAYAM – 638183

TAMILNADU.

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CERTIFICATES

EVALUATION CERTIFICATE

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Internal Examiner **External Examiner**

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DECLARATON

I do hereby declared that the dissertation **"FORMULATION DEVELOPMENT AND *INVITRO* EVALUATION OF FAST DISSOLVING TABLETS OF LERCANIDIPINE HYDROCHLORIDE BY DIRECT COMPRESSION METHOD: AN APROACH TO IMPROVING ORAL BIOAVAILIBILITY"** submitted to "**The Tamil Nadu Dr. M.G.R Medical University - Chennai",** for the partial fulfilment of the degree of **Master of Pharmacy** in **Pharmaceutics,** is a bonafide research work has been carried out by me during the academic year 2017-2018, under the guidance and supervision of **Mr. C. Kannan, M.Pharm.,** Assistant Professor, Department of Pharmaceutics, J.K.K. Nattraja College of Pharmacy, Kumarapalayam.

I further declare that this work is original and this dissertation has not been submitted previously for the award of any other degree, diploma, associate ship and fellowship or any other similar title. The information furnished in this dissertation is genuine to the best of my knowledge.

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Date: **Reg.no. 261610257**

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Dedicated to Parents,

Teachers &

My Family

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SYMBOL INDEX

Symbols		Explanation
Rpm	:	Revolutions per minute
°C	:	Degree celsius
Fig	:	Figure
E.g.	:	Example
Mg	:	Milligram
Min	:	Minutes
Ml	:	Milliliter
µg (mcg)	:	Microgram
µg/ml	:	Microgram per milliliter
%	:	Percentage
SDN	:	Standard deviation
R^2	:	Regression

CONTENTS

CHAPTER 1

INTRODUCTION

1. INTRODUCTION

The oral route of drug administration is the most important method for administering drugs for systemic effects. When a new drug is discovered, one of the first questions, a pharmaceutical company asks is whether or not the drug can be effectively administered by the oral route, for its intended effect. The development of dosage forms especially for the prolonged release purpose has been a challenge to formulation scientists, because of many independent factors governing the absorption of the drug from the gastrointestinal tract and competitive objectives, that is, any action taken toimprove one objective or set of objectives may cause another objective or set of objectives to degrade.

For example, modifying the solubility of the drug substance to prolong its release in the gastrointestinal tract may cause a reduction in the overall payload of formulation. A trial and error method of formulation does not allow the formulator to know how close a particular formulation is to the optimum solution, and finding the correct compromise is not straightforward and simple.

Hence a fast screen is needed, to enable them to formulate intelligently. For this purpose the drug substances are categorized into four classes based on their solubility parameter and permeability to bio-membranes, and such a classification system is called as a Biopharmaceutical Classification System (BCS). The BCS was first devised in 1995, by Amidon et al. and since then it has become a benchmark in the regulation of bioequivalence of oral drug products.

The BCS serves as a guiding tool for formulation scientists, for recommending a strategy to improve the efficiency of drug development by proper selection of dosage form and bioequivalence tests, to recommend a class of immediate release (IR) solid dosage forms, for which bioequivalence may be assessed based on in-vitro dissolution tests, and to lay the effect of excipients(s) on drug permeability.

The BCS guidance takes into account three major factors, dissolution, solubility, and intestinal permeability, which govern the rate and extent of drug absorption from immediate release solid dosage forms. The concept of BCS provides a better understanding of the relationship between drug release from the product and the absorption process. In this respect, the rate-limiting step is of primary relevance.

The bioavailability will be affected only by the in vivo performance of the dosage form, if dissolution/drug release is rate limiting for the dosage form. In contrast, as long as the permeation through bio-membranes is a rate- limiting process, bioavailability and bioequivalence are not so dependent upon the drug release behaviour of the dosage form.

Each class of the BCS is having its designated rate-limiting step and the possible tactics for its modification that enable the formulator to select and optimize a dosage form for the drug substance belonging to a particular class of BCS. The BCS has also been included in various guidance documents of regulatory importance.

1.1. Biopharmaceutical Classification System:

Biopharmaceutical Classification System1 (BCS) guidance was provided by US Food and Drug Administration (FDA), to improve the efficiency of drug product development process. According to which drugs are grouped into four major classes basing on their solubility and permeability.

1.2.Concept behind BCS:

The *in-vivo* performance of orally administered drugs depends upon their solubility and tissue permeability characteristics. The release rate or solubility of the drug substance will not be a governing parameter if the absorption of the drug is permeation rate limited and in such cases the *in- vitro* dissolution study can be used to demonstrate the bioavailability (BA) or bioequivalence (BE) of the drug product through *in*

vitro - in vivo correlation (IVIVC). On the other hand if absorption of the drug is dissolution rate limited that means the drug in the gastrointestinal fluid passes freely through the bio-membranes at a rate higher than it dissolves or is released from the dosage form.

The specifically designed *in-vivo* study will be required in such a case, to access the absorption rate, and hence its bioavailability and to demonstrate the bioequivalence ultimately. Such a drug substance is a good candidate for controlled delivery provided they qualify in terms of their pharmacokinetics and pharmacodynamics for controlled release development.

Also if a drug itself is having low solubility and a slow dissolution rate, the release will automatically get slower and the dosage form need not have an inbuilt release retardation mechanism, rather the absorption will now be governed by the gastric emptying rate.

Therefore, the dosage form must be able to restrain within the absorption window for a sufficient time so that absorption can take place. In such case, a hydrodynamically balanced (floating) system or a mucoadhesive dosage form will serve the purpose. Hence the BCS can work as a guiding tool for the development of various oral drug delivery technologies.

1.3.Characterization of Drug Moiety

For a drug substance to be positioned in the BCS, its solubility and tissue permeability characteristics must be known:

Solubility and Dissolution

Dissolution is a process by which a solid substance (drug) goes into the solution, that is, mass transfer of molecules from the solid surface to the liquid phase. The solubility is a property of substance by virtue of which it forms mixtures with other substances, which are chemically and physically homogeneous throughout. The degree of solubility (will be referred to as “solubility” hereafter) is the concentration

of the solute in a saturated solution (in equilibrium with solid/ drug) at any given temperature. The rate of dissolution and solubility are not the same. In contrast to solubility, the dissolution rate (i.e., the amount of solid substance that goes into the solution per unit time under standard conditions of temperature, pH, solvent composition, and constant solid surface area) is a dynamic process and better related to drug absorption and bioavailability. However, the rate of dissolution for a drug substance is proportionally related to its solubility in the dissolution medium. It has been investigated that unless a compound has aqueous solubility in excess of 1% (10 mg/ml) over the pH range 1-7 at 37°C potential bioabsorption problems may occur, and if the intrinsic dissolution rate is greater than 1 mg/cm2 /min then the absorption remains unimpeded.

a) Determination of Solubility

The solubilities are determined by exposing an excess of solid (drug) to the liquid in question (water/buffer) and assaying after equilibrium has been established. It usually takes 60 to 72 hours to establish equilibrium; sampling at earlier points is necessar y. Solubilities cannot be determined by the precipitation method because of the so-called metastable (solubility) zone. The pH solubility profile of the drug is determined at 37 ± 10°C in the aqueous medium, with pH in the range of 1 -7.5. A sufficient number of samples should be evaluated,to accurately define the pH solubility profile. A minimum of three replicate determinations of solubility in each pH condition should be carried out. Standard buffer solutions described in pharmacopoeia (B.P. 2003) are considered appropriate for use in solubility studies. The concentration of the drug substance in the selected buffer or pH condition should be determined using a validated solubility-indicating assay that can distinguish the drug substances from their degradation products.

b) Determination of Permeability

Permeability along with solubility forms the backbone of BCS that helps in accessing oral absorption of drug molecules.

The various methods used for permeability screening are as mentioned below:

1. Determination of o/w pH partition profile of the drug
2. Studies of the extent of absorption inhumans - Pharmacokinetic mass balance and absolute bioavailability studies
3. Intestinal permeability studies - The following tissues can be used:
    i) *In-vivo* intestinal perfusion studies in human
    ii) *In-vivo* or *in-situ* perfusion studies in animals
4. *In vitro* permeation studies using excised human or animal intestinal tissue
5. *In-vitro* permeation experiments across a monolayer of cultured human intestinal cells
6. *Caco cell lines* are derived from human colon carcinoma and used widely for permeability determination. The technique is expensive and requires specialized skills. Caco2 cell lines are about 60% accurate in predicting human permeability/absorption.
7. Initial screening can also be carried out using parallel artificial membrane permeability analysis (PAMPA), which is carried out on microplates. It measures the permeation of compounds through a phospholipid-coated filter medium that mimics intestinal cell structures.

1.4.Class Boundaries used in BCS

1. A drug substance is considered highly soluble when the highest dose strength is soluble in ₤ 250 ml water over a pH range 1 to 7.5.
2. A drug is considered highly permeable when the extent of absorption in humans is determined to be 90% of an administered dose, based on the mass balance or in comparison to an intravenous dose.

3. A drug product is considered to dissolve rapidly when 85% of the labeled amount of drug substance dissolves within 30 minutes, using USP apparatus I or II in a volume of 900 ml buffer solution.

1.5.Selection of Dissolution Media

The dissolution medium selected must be able to reflect the *in-vivo* conditions, to give a better *in vitro - in vivo* correlation (IVIVC). However the bile salts are present in the small intestine even in a fasted condition (average concentration @ 5 mM), standard buffer solutions have been used widely in the solubility analysis for BCS. In an attempt to duplicate the intestinal conditions *in-vitro,* two kinds of media have been designed, one to simulate the fasted state small intestine and the other to simulate fed state conditions in the small intestine. These two dissolution media can be used in drug discovery and development and are acceptable in regulatory aspects too.

Hence for the drugs belonging to Class I and Class III (i.e.,having high solubility), simple aqueous dissolution media such as simulated gastric fluid (SGF, without enzymes) or simulated intestinal fluid (SIF, without enzymes) are suggested. In contrast, for Class II and IV (i.e., drugs with low solubility), use of biorelevant media is recommended for dissolution testing. For example:

- To simulate fasting stomach condition - SGF plus surfactants
- To simulate fed state condition – Milk with 3.5% fat
- For fasted intestine -Low volume SIF. (For poorly soluble drugs)
- For fed intestine – High volume SIF. (For poorly soluble weak acid drugs).

The intrinsic dissolution rate can also be used as an alternative in BCS, especially in a case when the solubility of a drug cannot be accurately determined. Addition of a surfactant like *sodium lauryl sulfate (SLS)* or other surfactants may be required to mimic the solubilization *in-vitro*. For example, the recommended

USP dissolution media for medroxy progesterone acetate tablet, danazol capsule, carbamazepine tablet, and flutamide tablet contain 0.5%, 0.75%, 1.0% and 2.0% SLS (USP26-NF21S1). Further research is required to explore the proper selection of dissolution of media and to develop a uniform media reflecting the *in-vivo* dissolution condition.

Class I: High Permeability and High Solubility

Ex: Propranolol, Metoprolol,Diltiazem, Verapamil

Class II: High Permeability and Low Solubility

Ex: Ketoconazole, Mefenamic acid, Nifedipine, Nicardipine, Felodipine, Piroxicam

Class III: Low permeability and High solubility

Ex: Acyclovir, Neomycin B, Captopril, Enalaprilate, Alendronate.

Class IV: Low permeability and Low solubility

Ex: Chlorthiazide, Furosemide, Tobramycin.

1.6.Purpose of the BCS Guidance

1. Expands the regulatory application of the BCS and recommends methods for classifying drugs.
2. Explains when a waiver for in vivo bioavailability and bioequivalence studies may be requested based on the approach of BCS.

1.7.Goals of the BCS Guidance

1. To improve the efficiency of drug development and the review process by recommending a strategy for identifying expendable clinical bioequivalence tests.
2. To recommend a class of immediate- release (IR) solid oral dosage forms for which bioequivalence may be assessed based on in vitro dissolution tests.
3. To recommend methods for classification according to dosage form dissolution, along with the solubility and permeability

characteristics of the drug substance. The classification is associated with drug dissolution and absorption model, which identifies the key parameters controlling drug absorption as a set of dimensionless numbers:

4. **The Absorption Number (An)** is the ratio of the Mean Residence Time (Tres) to the Mean Absorption Time (Tabs) and it could be estimated using equation.

An = (Tres / T abs) = (3.14R2L/Q) (R/Peff) ..... . (2)

5. **The Dissolution number** is a ratio of mean residence time to mean dissolution time. It could be estimated using equation 2.
6. **The Dose number** is the mass divided by an uptake volume of 250 ml and the drug's solubility. It could be estimated using equation 2.

D0 = Dose/(V0 xC mins) .....(4)

7. **The mean residence time:** here is the average of the residence time in the stomach, small intestine and the colon.

Where: L = tube length, R = tube radius, π =3.14, Q =fluid flow rate, ro = initial particle radius, D = particle acceleration, ρ = particle density, Peff = effective permeability, Vo is the initial gastric volume equal to 250 ml which is derived from typical bioequivalence study protocols that prescribe administration of a drug product to fasting human volunteers with a glass of water at the time of drug administration and Cs min is minimum aqueous solubility in the physiological pH range of 1-8.

Techniques for Solubility Enhancement.

1) Chemical Modification

1. Salt Formation
2. Co-crystallization
3. Co-solvency
4. Hydrotropic
5. Solubilizing agent

6. Nanotechnology

2) Physical Modifications

1. Particle size reduction
2. Modification of the crystal habit
3. Complexation
4. Solubilization by surfactants
5. Drug dispersion in carriers
    a. Solid solution
    b. Eutectic mixtures
    c. Solid dispersion

3) Other

1. Supercritical fluid method
2. Spray freezing into liquid and Lyophillization
3. Evaporative precipitation into aqueous solution
4. Solvent evaporation method
5. Hot melt extrusion
6. Electrostatic spinning method
7. Direct capsule filling
8. Polymeric Alteration
9. High- Pressure Homogenization
10. Lyophilization technique
11. Inclusion Complexes:
    a) Kneading Technique
    b) Co-precipitation
    c) Neutralization
    d) Co-grinding
    e) Spray-Drying Method
    f) Microwave Irradiation Method

1.8.Extension to BCS: (BCS containing six classes)

Bergstrom et al. devised a modified Biopharmaceutical Classification System, in which they categorized the drugs into six classes based on the solubility and permeability. The solubility was classified as “high” or “low” and the permeability was allotted as “low”, “intermediate,” or “high”. This new classification was developed based on the calculated surface area descriptors on the one hand and solubility and permeability on the other. Surface areas related to the nonpolar part of the molecule resulted in good predictions of permeability. It was tentatively concluded that these models would be useful for early indication with regard to the absorption profiles of the compound during the early stages of drug discovery so that the necessary modifications can be made to optimize the pharmacokinetic parameters.

1.9.Application of BCS in Oral Drug Delivery Technology

Once the solubility and permeability characteristics of a drug are known, the formulation scientist can then, based on BCS, easily decide which drug delivery technology will best help in getting the optimum pharmacokinetic characteristics. The major challenge in the development of drug delivery systems for a class I drug is to achieve a targeted release profile associated with the particular pharmacokinetic and pharmacodynamic properties. Formulation approaches include both the control of release rate and physiochemical properties of drugs like the pH-solubility profile of the drug.

The systems that are developed for class II drugs are based on the micronization, lyophilization, addition of surfactants, formulation as emulsions and microemulsion systems, use of complexing agents like cyclodextrins, and so on. Class III drugs are required for technologies that address the fundamental limitations of absolute or regional permeability. Peptides and proteins constitute, solely, the class III drugs; these are now the center of focus for research in drug delivery. The class

IV drugs present a major challenge for the development of drug delivery systems and the route of choice, due to their poor solubility and permeability characteristics. These are often administered by parenteral route with the formulation containing solubility enhancers.

1.10.BCS as a Framework for Optimization of a New Chemical Entity

The BCS provides a clue about the pharmacokinetics of the drug (NCE), any newly synthesized or identified chemical molecule that is proved to be therapeutically active, but is still under investigation for formulation development and final approval, which provides an opportunity to the synthetic chemist or the drug designer to manipulate in the chemical structure of the drug entity so as to optimize the physicochemical parameters of the lead molecule for desired drug delivery and targeting characteristics.

The synthetic chemist and formulation scientists act together toachieve better 'deliverability' directed toward the desired pharmacokinetics and therapeutic efficiency right from the initial stages of drug design, to fulfill the propelled need for "High Throughput Pharmaceutics (HTP)". Lipinski *et al.* has suggested a 'rule of 5,' which has been widely adopted by the pharmaceutical industry as a yard stick for screening out compounds that are likely to have poor absorption profiles. According to this rule the poor absorption or permeation is more likely when:

- There are more than five H-bond donors (expressed as a sum of hydroxyl and N-H linkage).
- The molecular weight of the drug moiety is more than 500
- The log P is over %
- There are more than 10 H-bond acceptors

Compounds that are substrates for the biological transporters are an exception to the rule.

1.11.Mouth dissolving tablet (MDT):

Mouth dissolving tablet (MDT) It is a tablet that disintegrates and dissolves rapidly in the saliva, within a few seconds without the need of drinking water or chewing. A mouth dissolving tablet usually dissolves in the oral cavity within 15s to 3 min. Most of the MDTs include certain super disintegrants and taste masking agents.

Ideal properties of MDT:

A Mouth Dissolving Tablet should

a. Not require water or other liquid to swallow.
b. Easily dissolve or disintegrate in saliva within a few seconds.
c. Have a pleasing taste.
d. Leave negligible or no residue in the mouth when administered.
e. Be portable and easy to transport.
f. Be able to be manufactured in a simple conventional manner within low cost.
g. Be less sensitive to environmental conditions like temperature, humidity etc.

Advantages of MDT:

a. No need of water to swallow the tablet.
b. Can be easily administered to pediatric, elderly and mentally disabled patients.
c. Accurate dosing as compared to liquids.
d. Dissolution and absorption of drug is fast, offering rapid onset of action.
e. Bioavailability of drugs is increased as some drugs are absorbed from mouth, pharynx and esophagus through saliva passing down into the stomach
f. Advantageous over liquid medication in terms of administration as well as
g. transportation

h. First pass metabolism is reduced, thus offering improved bioavailability and thus reduced dose and side effects.
i. Free of risk of suffocation due to physical obstruction when swallowed, thus
j. offering improved safety.
k. Suitable for sustained/controlled release actives.
l. Allows high drug loading.

1.12.Methods for the Formulation of Mouth Dissolving Tablets

Various processes employed in formulating MDTs are described below.

A.Patented Technologies

1. Zydus Technology

This technology involves physical trapping of drug in a matrix composed of a saccharide and a polymer .The polymer generally used are partially hydrolyzed gelatin, hydrolyzed dextran, dextrin, alginate, polyvinyl alcohol, polyvinyl pyrrolidone, acacia and these mixtures. The methodology involves solution or dispersion of components is prepared and filled in to blister cavities, which are frozen in a liquid nitrogen environment. The frozen solvent is removed or sublimed to produce porous wafers. Peelable backing is used to pack zydis units. These formulations are sensitive to moisture and may degrade at humidity greater than 65% zydis is patented by R.P. Scherer.

2. LYOC

Oil in water emulsion is prepared and placed directly in to blister cavities followed by freeze drying. Non homogeneity during freeze drying is avoided by incorporating inert filler to increase the viscosity finally the sedimentation. The methodology is patented by pharmalyoc.

3. Quick Solv

Methodology includes dissolving matrix components in water and the solution or dispersion is frozen. Then dry the matrix by removing

water using an excess alcohol (solvent extraction). The product formed has uniform porosity and adequate strength for handling. This technology patented by Jassen Pharmaceuticals.

4. Nanocrystal Technology

Nano crystal technology includes lyophilization of colloidal dispersion of drug and water soluble ingredients filled into blister pockets. This method avoid manufacturing process such as granulation, blending and tableting. This method is advantageous for highly potent and hazards drugs, manufacturing losses are negligible and the process is small quantities of drugs. This methodology is patented by Elanking of Prussia.

5. Flash Tab Technology

This technology includes granulation of excipients by wet granulation method and follow by compressing in to tablets excipients used in this technology are of two types. Disintegrating agents include reticulated polyvinyl pyrolidone or carboxy methyl cellulose, starch, modified starch, microcrystalline cellulose, carboxy methylated starch, etc. tablets formed have satisfactory physical resistance. Disintegration time is within 1 minute. This methodology patented by Ethypharm, France.

6. Orasolv Tecnology

This includes use of effervescent disintegrating agents compressed with low pressure to produce MDTs. The evaluation of carbon dioxide from the tablet produces fizzing sensation, which is a positive organoleptic properties. Concentration of effervescent mixed usually employed is 20-25%of tablet weight .as the tablets prepared at low compression force, they are soft and fragile in nature. This is initiated to develop paksolv, a special packaging to protect tablets during storage and transport. Paksolv is dome-shaped blister package, which

prevents vertical movements of tablets in the depression. This offers moisture, light and child resistance packing.

7. Durasolv Tecnology

This methodology utilized conventional tableting equipment and tablets are formulated by using drug non-direct compression fillers and lubricants. Non direct compression fillers are dextrose mannitol, sorbitol, lactose, and sucrose which have advantages of quick dissolution avoid gritty structure (which is generally present in direct compressible sugar)The tablets formed are strong and can be packed in conventional packing in bottles and blisters. Nondirect compressible fillers generally used in the range of 60-95%,lubricants in 1-2.5%.this technology patented by CIMA labs. Durasolv products include Nulev (hyoscyaminesulphate),Zoming ZMT(Zolmitraptan).

8. Wow Tab Tecnology

This technology utilizes conventional granulation and tableting methods to produce MDTs employing low-and high moldability saccharides. WOW means with out water. Low moldabilty saccharides are lactose, mannitol, glucose, sucrose and xylitol. High moldability saccharides are maltose, maltitol, sorbitol and oligosaccharides. When these two type saccharides used alone tablets obtained do not have desired properties of rapid disintegration and hardness, so combination are used. This technology involves granulation of low-moldable saccharieds as a binder and compressing in to tablets followed by moisture treatment. So the tablets formed showed adequate hardness and rapid disintegration .this technology patented by Yamanouchi. WOW tab product include Benadryl allergy and sinus fast melt (OTC).

9. Dispersible Tablet Tecnology

It offers development of MDT improved dissolution rate by incorporating 8-10% of organic acid and disintegrating agents. disintegrating agents facilitates rapid swelling and good wetting results

in quick disintegration. Disintagrants include starch, modified starches, microcrystalline cellulose, alginic acid, cross linked sodium carboxy methyl cellulose and cyclodextrines. Combilnation of disintegarants improved disintegration usally less than 1 minutes. The methodology patented lek, Yugoslavia.

10. Pharma Burst Tecnology

It utilize co proceed exicipients to develop MDT which dissolves within 30-40 seconds. The technology involves dry blending of drugs, flavor and lubricant followed by compression in to tablets. The tablets obtained have sufficient strenghth so they can be packed in blister packs and bottles. This technology patened by SPI pharma, new castle.

11. Frosta Technology

It utilizes the concept of formulating plastic granules and compressing at low pressure to produce strong tablets with high porosity. Plastic granules composed of porous and plastics material, water penetration enhancer and binder. The process involves mixing the porous plastic material with water penetration enhancer and followed by granulating with binder. The product showed excellent hardness and rapid disintegration within 15-30 seconds. This methodology patented by Akina.

12. Oraquick

It utilize taste masking microspheres technology called as micro mask, which provides superior mouth feel, significant mechanical strength and quick disintegration and dissolution of the products. This process involves preparation of micro particles in the form of matrix that protects the drug which can be compressed with sufficient mechanical strength. Low heat of production in this process make it suitable for heat sensitive drug. The products formed dissolves within few seconds. The methodology patented by K.V Pharmaceuticals.

13. Ziplets or Advatab

It utilize water insoluble gradients combined one are more effective disintegrants to produce MDT s with improved mechanical strength and optimum disintegration time at low compression force. Advantage of the method include high drug loading, formation of coated particles and does not require special packaging. This technology patented by pessano con Bornago.

14. Flashdose

The flash dose tablets consists of self binding shear form matrix termed as floss. Shear form matrices are prepared by flash heat processing. This technology patented by Fluzisz. Egibuprofen melt in mouth tablets.

B.Conventional Methods

1. Lyophilization or Freeze-Drying

Lyophilization is a process which includes removal of a solvent from a frozen suspension of drug with structure forming additives. Freeze drying of a drug along with additives imparts glossy amorphous structure resulting in highly porous and light weight product. The resulting tablet has rapid disintegration and dissolution when placed on a tongue and the freeze dried leutin dissolves instantly to release the drug. MDT s formed by lyophilization have some demerits like low mechanical strength, poor stability at higher temperature and humidity. Use of expensive equipment for freeze drying is another demerits of the process.

2. Moulding

Molding process include moistening, dissolving or dispersing the drug with a solvent then molding the moist mixer in to tablets(compression molding with a low pressure than conventional tablet compression)evaporating the solvent from drug solution, or suspension at ambient pressure respectively. The molded tablets formed

by compression molding are air dried. As the compression force employed is lower than conventional tablet, the molded tablet results in highly porous structure, which increase the disintegration and dissolution of the product. To further improve the dissolution rate of the product powder mixer should be sieved through very fine screen. This process is applied usually with soluble ingredients (saccharides) which offer improved mouth feel and disintegration of tablets. Some of the demerits observed are the tablet formed by this process shows low mechanical strength, which results in erosion and breakage during handling.

3. Cotton Candy Process

Cotton candy process involves formation of matrix of polysaccharides or saccharides by simultaneous action of flash melting and spinning. The matrix formed is partially recrystallized to have improved flow properties and compressability. This candy floss matrix is then milled and blended with active ingredients and excipients and subsequently compressed to MDTs. This process is so named because it utilizes a unique spinning mechanism to produce floss-like crystalline structure, which mimic cotton candy. The main merits of this method are the process can accommodate high doses of drug and offers improved mechanical strength. The main demerit is the use of high process temperature.

4. Spray Drying

In this method MDTs formulated by using hydrolyzed / unhydrolyzed gelatin as supporting agent for matrix, mannitol as bulking agent and sodium starch glycolate or croscarmellose sodium as disintegrating agent. Disintegration and dissolution were further improved by adding effervescent components.ie citric acid (an acid) and sodium bicarbonate (an alkali). The formulation was spray dried to yield a porous powder. The products formed are highly porous fine powders

and are disintegrated in<20 seconds. Allen et al utilized this method for preparing MDTs.

5. Mass Extrusion

It involves softening the active blend using the solvent mixture of water soluble polyethylene glycol and methanol and subsequent expulsion of softened mass through the extruder or syringe to get a cylinder of the product in to even segments using heated blade to forms tablets**. (yadav A.V et al,2010)**

6. Compaction Melt Granulation

The method involves incorporation of hydrophilic waxy binder (super poly state.) PEG -6-sterate. Super poly state is a waxy material with an M.P of 33-37c. and an hydrophilic lipophilic balance of 9. It act as binder, increase the physical resistance of tablets and it helps the disintegration of tablets as it melt in the mouth and solubilizes rapidly leaving no residue. Super poly state incorporated in the formula by melt granulation method, where granules are formed by the molten form of the material. eg crystallized paracetamol was used as model drug and in addition mannitol added as water soluble excipient and cross carmellose sodium as disintegrating agents. Abdlbary *et al* prepared MDT by this method.

7. Phase Transition Process

Kuno *et al* investigated disintegration of MDTs are formulated by sugar alcohols using erythriol (M.P 122C), xylitol (m.p 93-95), trehalose (97c) and mannitol (166c). This method involves compressing a powder containing two sugar alcohols with high and low-melting points and subsequent heating at temperature between their melting points. Before heating process the tablet do not have sufficient hardness because of low compatibility. The tablet hardness was increased after heating process, due to the increase of interparticular bonds or bonding surface area in tablets induced by phase transition of low melting point sugar alcohols.

8. Sublimation

The method involves addition of volatile salt to the tableting components, mixing and volatilizing the volatile salt creates pores in the tablets come in contact with saliva. Camphor, naphthalene, urea, ammonium bi carbonate etc., can be used to prepare porous tablets of good mechanical strength. koizumi et al used mannitol as diluents and camphor as volatile material to prepare porous compressed tablet. The tablets were subjected to vaccum at 80 c for 30 minutes to eliminate camphor and thus form the pores in the tablet. The tablet formed have highly porous matrix which is the key factor for rapid disintegration.

C.Other Methods

Other methods includes dry granulation, wet granulation and direct compression methods. The important components used in these methods are super disintegrants.

1. Dry Granulation

In this technique there is no use of liquids. The process involves the formation of slugs. Then slugs are screened are milled to produce granules. The granules formed are then compressed to form tablet.

2. Wet Granulation

The process involves addition of liquids to a powder in a vessel equipped with any type of agitation that will produce agglomeration or granules. These granules after drying are compressed to form tablets. This method have more operational manipulation and is more time consuming than other methods. this method is not suitable for drugs which ass thermo labile or hydrolysable by presence of water in the liquid binder.

3. Direct Compression

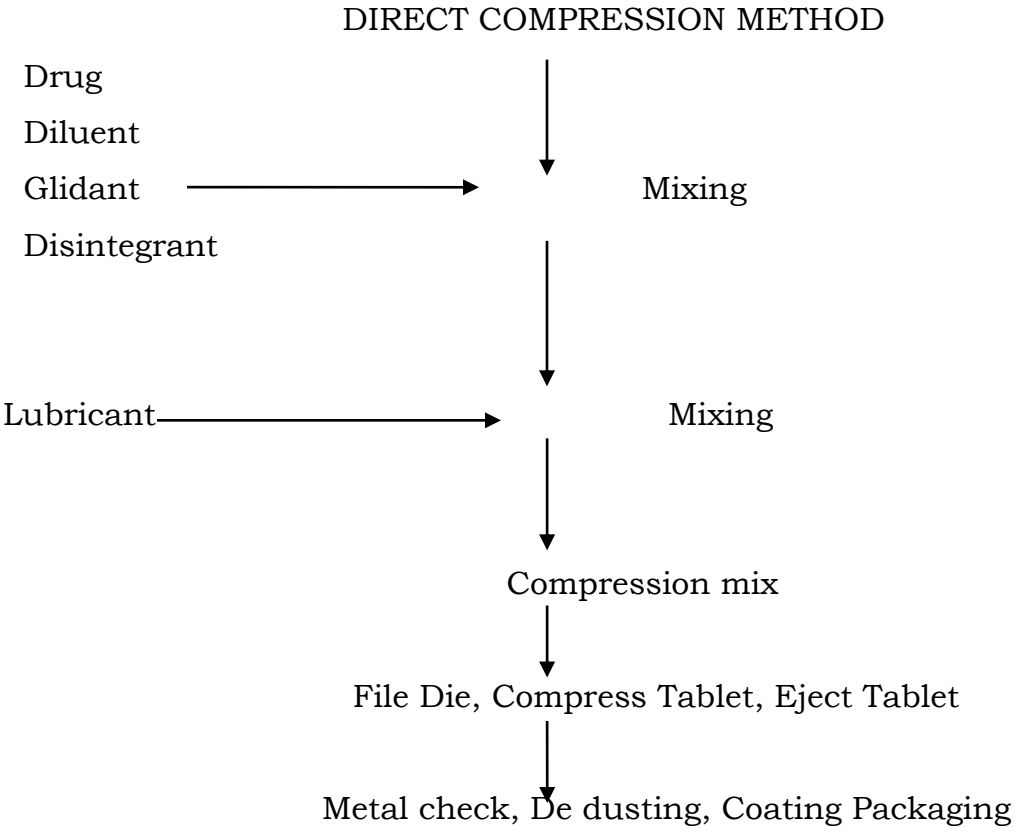
In direct compression method, of powder blends of active ingredients and suitable excipients, which will flow uniformly in the die cavity and formed a film compact (**Banker G.S et al 1987**).direct

compression method are very popular because it reduse the number of steps involved and the materials required.

Advantages

1. Easiest method to manufacture fast dissolving tablets.
2. Low manufacturing cost.
3. Use of conventional equipment and commonly available excipients.
4. High quality finished product.

Fig.No. 1: Flow sheet of direct compression



1.13.Super Disintegrants in Immediate Release Tablets

Super-disintegrants are effective at low concentration and have greater disintegrating efficiency and they are effective intra-granularly as well as extra-granularly. But have one drawback that it is hygroscopic therefore not used with moisture sensitive drugs. These super-disintegrants act by swelling and due to swelling pressure exerted in the

outer direction or radial direction, it causes tablet to burst or accelerate the absorption of water leading to an enormous increase in the volume of granules to promote disintegration is shown in Fig 2.

Fig.No. 2: Mechanisms of Super-disintegrant swelling

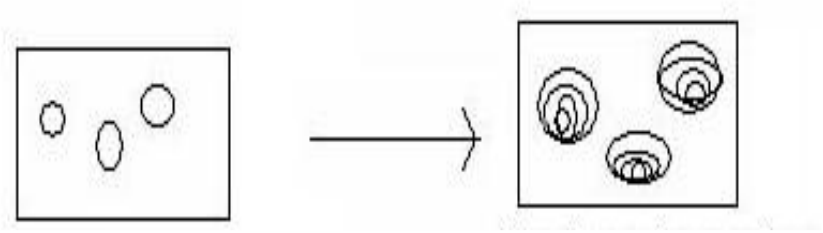


Table.No. 1: LIST OF SUPERDISINTEGRANTS

SUPERDISINTEGRANTS	TYPE	MECHANISM OF ACTION	SPECIAL COMMENTS
Croscarmellose Ac-Di-Sol Nymce ZSX Primellose Solutab Vivasol	Crosslinked Cellulose	Swells 4-8 folds in < 10 seconds Swelling and wicking both.	Swells in two dimensions. Direct compression or Granulation Starch free
Crospovidone Crospovidon M Kollidon Polyplasdone	Crosslinked PVP	Swells very little and returns to original size after compression but act by capillary action	Water insoluble and spongy in nature so get porous tablet
Sodium starch glycolate Explotab Primogel	Crosslinked Starch	Swells 7-12 folds in <30 seconds	Swells in three dimensions and high level serve as sustain release matrix
Alginic acid NF Satialgine	Crosslinked alginic acid	Rapid swelling in aqueous medium or wicking action	Promote disintegration in both dry or wet granulation

Table. No. 2: PARAMETERS INFLUENCING THE SWELLING BEHAVIOUR OF SUPERDISINTEGRANTS [6-8]

PARAMETERS	EFFECTS
Amount of superdisintegrant	A minimum amount of superdisintegrant is necessary for the development of sufficient swelling to outer membrane
Additives (binders)	Polymeric binders can reduce swelling pressure by spacial separation of superdisintegrant particles or competition for free water
Ionic strength of the medium	Competition of the ions for free water
pH values	Swelling can be influenced for the superdisintegrants with ionizable groups(e.g:carboxylic groups in croscarmellose)

1.14.Effect of excipients used in the Formulation:

a) Effect of fillers:

The solubility and compression characteristics of fillers affect both rate and mechanism of disintegration of tablet. If soluble fillers are used then it may cause increase in viscosity of the penetrating fluid which tends to reduce effectiveness of strongly swelling disintegrating agents and as they are water soluble, they are likely to dissolve rather than disintegrate. Insoluble diluents produce rapid disintegration with adequate amount of disintegrants. Tablets made with spray dried lactose (water soluble filler) disintegrate more slowly due to its amorphous character and has no solid planes on which the disintegrating forces can be exerted than the tablet made with crystalline lactose monohydrate.

b) Effect of binder:

As binding capacity of the binder increases, disintegrating time of tablet increases and this counteract the rapid disintegration. Even the concentration of the binder can also affect the disintegration time of tablet.

c) Effect of lubricants:

Mostly lubricants are hydrophobic and they are usually used in smaller size than any other ingredient in the tablet formulation. When the mixture is mixed, lubricant particles may adhere to the surface of the other particles. This hydrophobic coating inhibits the wetting and consequently tablet disintegration. Lubricant has a strong negative effect on the water uptake if tablet contains no disintegrants or even high concentration of slightly swelling disintegrants. On the contrary, the disintegration time is hardly affected if there is some strongly swelling disintegrant present in the tablet.

1.15.Methods of addition of Disintegrants:

Disintegrating agent can be added either prior to granulation (intragranular) or prior to compression (after granulation i.e. extragranular) or at both processing steps.

Extragranular fraction of disintegrant (usually, 50% of total disintegrant requires) facilitates breakup of tablets to granules and the intragranular addition of disintegrants produces further erosion of the granules to fine particles.

CHAPTER 2

LITERATURE REVIEW

2. LITERATURE REVIEW

1. **Gupta *et al.,*** described on "Fast Dissolving Tablet- A Review". This review describes the various formulation aspects, superdisintegrants employed and technologies developed for MDTs, along with various excipients, evaluation tests, marketed formulation and drugs used in this research area.
2. **Chawla *et al.,*** described on "Mouth Dissolving Tablets: An Overview". These overview deals with the gold standard in pharmaceutical industry are the oral delivery because it is the easiest, safest, economical and convenient method for the drug delivery. Mouth dissolving tablets have becomes the most demanding application during last decades and in the pharmaceutical industry this field has become a rapidly area. Mouth dissolving tablets during insertion in the mouth should have to dissolve or disintegrate in the mouth within 15sec to 3 minutes without the help or need of any drinking agent like water. These mouth dissolving tablets can be given anytime, anywhere to anyone who needs this without the presence of water and these will show the effective action in few minutes.
3. **Gandhi *et al.,*** studies "Mouth Dissolving Tablets: A New Venture in Modern Formulation Technology". This review describes the various formulation aspects and technologies developed for MDTs, along with various excipients, evaluation tests, marketed formulations of MDTs. There are multiple fast dissolving OTC and Rx products on the market, most of which have been launched in the past 3 to 4 years. There have also been significant increases in the number of new chemical entities under development using a fast-dissolving drug delivery technology. Thus, in future, it is expected that this delivery system will get much importance as that of conventional delivery systems.

4. **Bhanja *et al.,*** studied the "Mouth Dissolving Tablets of Losartan Potassium: Formulation and Evaluation". The objective of the proposed research work is to prepare and evaluate the mouth dissolving/disintegrating tablets (MDTs) of losartan Potassium, which avoid the first-pass metabolism, improved the dissolution rate and enhance the bioavailability. Mouth dissolving tablets (MDTs) were prepared by direct compression method by using combination of superdisintegrant like Ac-Di-Sol and Polyplasdone-xl (1%,2%,3%&4%). and evaluated for physico-chemical evaluation parameter such as hardness, friability, weight variation, drug content uniformity, water absorption ratio, wetting time, in-vitro and in-vivo disintegration time, *in-vitro* dissolution studies. The twelve formulations, B1to B8 were formulated and among these formulations, B8 was optimized.
5. **Shah *et al.,*** described on "Formulation Development and Evaluation of Mouth Dissolving Tablet of Tramadol Hydrochloride". The aim of this study was to formulate FDTs with sufficient mechanical integrity and to achieve faster disintegration in the oral cavity without water. To achieve this goal, mannitol used as diluent and aspartame as sweetening agent for the formulation of tablets. Attempts were made to enhance dissolution rate along with faster disintegration using superdisintegrants, like croscarmellose sodium, sodium starch glycolate and crospovidone. Tramadol hydrochloride, a centrally acting synthetic opioid analgesic, was selected as the active pharmaceutical ingredient in the study.
6. **Kalia *et al.,*** studied the "Formulation and Evaluation of Mouth Dissolving Tablets of Oxcarbazepine". The present investigation was undertaken with a view to develop mouth-dissolving tablets of oxcarbazepine, which offers a new range of product having desired characteristics and intended benefits. In this study, the mouth dissolving tablets were prepared using two different technologies,

direct compression method and solid dispersion technology. Tablets produced by direct compression method contain crospovidone as a superdisintegrant and aspartame as a sweetener. Oxcarbazepine solid dispersions with polyvinylpyrrolidone K-30 in 1:2 ratios of drug: carrier showed maximum drug release and hence, compressed along with other excipients into mouth dissolving tablet. The results compared for both the technologies showed that the oxcarbazepine tablets prepared using solid dispersion technology was found to have good technological properties and satisfying and reproducible drug dissolution profiles.

7. **Kaur *et al.,*** focused on "Mouth Dissolving Tablets: A Novel Approach to Drug Delivery". This review focused on Recent advances in Novel Drug Delivery Systems (NDDS) aim for designing dosage forms, convenient to be manufactured and administered, free of side effects, offering immediate release and enhanced bioavailability, so as to achieve better patient compliance. Though oral drug delivery systems, preferably, tablets are the most widely accepted dosage forms, for being compact, offering uniform dose and painless delivery. This is seen to afflict nearly 35% of the general population and associated with a number of conditions, like parkinsonism, mental disability, motion sickness, unconsciousness, unavailability of water etc. To overcome such problems, certain innovative drug delivery systems, like 'Mouth Dissolving Tablets' (MDT) have been developed.
8. **Ashish *et al.,*** studied the "Mouth Dissolving Tablets: A Review". This current paper studied the MDTs were developed with an aim of having sufficient hardness, integrity and faster disintegration without water. Some tablets are designed to dissolve in saliva remarkably fast, within a few seconds, and are true fast-dissolving tablets. Others contain agents to enhance the rate of tablet disintegration in the oral cavity, and are more appropriately termed fast-disintegrating tablets, as they may take up to a minute to completely disintegrate.

This tablet format is designed to allow administration of an oral solid dose form in the absence of water or fluid intake. Such tablets readily dissolve or disintegrate in the saliva generally within <60 seconds.

9. **Prasanthi *et al.,*** studied the "Formulation and Evaluation of Sitagliptin Phosphate and Simvastatin Bilayered Tablets". In general the work deals with the combine formulation and evaluation of bilayered tablets of DPP-4 inhibitor i.e., sitagliptin phosphate and HMG-CoA reductase i.e., simvastatin. Ten formulations of sitagliptin phosphate and simvastatin bilayered tablets were prepared by varying the ratios of polymers in the sitagliptin phosphate layer and simvastatin layer F1 to F10 by direct compression method. FTIR studies revealed there is no interaction between the drugs i.e., sitagliptin phosphate and simvastatin and the polymers such as pregelatinised starch, potato starch and sodium starch glycolate. The physical appearance was good and elegant. The weight variation, friability and hardness of tablets were found to be within USP limits. In-vitro drug release for sitagliptin phosphate and simvastatin of all formulations of F1 to F10 was carried out in phosphate buffer pH 6.8 dissolution media. Among all the formulations F7 was optimized as best formulation.
10. **Heda *et al.,*** worked on "Development of Granisetron Hydrochloride Fast Dissolving Tablets". The purpose of study was development of fast dissolving Granisetron Hydrochloride (GRA) tablets using suitable disintegrating agent. Comparative effect of incorporation of superdisntegrants and conventional disintegrant at same concentrations, on disintegration and dissolution was studied. The superdisintegrants used were sodium starch glycolate (SSG) and Kyron_ T-314 (Polacrillin potassium) while sodium alginate (SA) was used as representative conventional disintegrant. The tablets were prepared by wet granulation method. The disintegration times were lower and dissolution profile of GRA was comaparatively better with

the batches containing SSG compared to other disintegrating agents. The granisetron tablets with 3% SSG shows lower disintegration time than Kyron_ T-314 and SA.

11. **Patil *et al.,*** studie the "Formulation and Evaluation of Fast Dissolving Tablets of Granisetron Hydrochloride by Dry Grnulation Method". The aim of work is to characterization and evaluation of fast dissolving tablet of Granisetron hydrochloride using three superdisintegrants like crosscarmellose sodium, crosspovidone and sodium starch glycolate. FTIR studies revealed that there was no physico-chemical interaction between granisetron hydrochloride and other excipients. The tablets were prepared by dry granulation method and all had the same amount of ingredients except, the superdisintegrant level. Tablet containing crosspovidone showed excellent disintegration time and drug release as compared to other formulations.
12. **Reichal *et al.,*** described on "Design and Evaluation of Fast Dissolving Tablets of Sitagliptin Phosphate Monohydrate". The core objective of the study was to design and evaluate fast dissolving tablets of Sitagliptin Phosphate Monohydrate. Fast dissolving or disintegrating tablets were prepared by wet granulation by using starch Glycolate, Microcrystalline Cellulose, Cross carmellose Sodium as superdisintegrants. The prepared tablets were evaluated for pre - compression and post compression parameters. The in-vitro release studies were carried out by using USP Type II dissolution apparatus. The selected optimized batches were kept for stability studies at 40 °C /75%± 5%RH for a period of three months. All the results obtained were found to be satisfactory and within the limits. The results of in-vitro drug release study showed that formulation F6 exhibited good and fast disintegrating time within 12 seconds.
13. **Nagendrakumar *et al.,*** studied on "Design of Fast Dissolving Granisetron Hcl Tablets Using Novel Co –Processed

Suprdisintegrants". In the present work, fast dissolving tablets of granisetron HCl were prepared using novel co-processed superdisintegrants consisting of crospovidone and sodium starchglycolate in the different ratios (1:1, 1:2 & 1:3). The developed superdisintegrants were evaluated for angle of repose, Carr's index and Hausner's ratio in comparison with physical mixture of superdisintegrants. The angle of repose of the developed excipients was found to be < 25o, Carr's index in the range of 10-15% and Hausner's ratio in the range of 1.11-1.14. Based on *in vitro* dispersion time (approximately 20 sec), promising formulation CP1 was tested for *in vitro* drug release pattern in pH 6.8 Phosphate buffer and short-term stability (at 400C/75% RH for 3 months), drug excipients interaction (IR spectroscopy) were studied. Among the designed formulations, the formulation (CP1) containing 4% w/w of co-processed superdisintegrant (1:1 mixture of crospovidone and sodium starchglycolate) emerged as the overall best formulation (t50% 2.0 min) based on drug release characteristics in pH 6.8 phosphate buffer compared to commercial conventional tablet formulation (t50% >15 min).

14. **Keerthi *et al.,*** described on "Formulation and Evaluation of Sitagliptin Phosphate Gastro Retentive Tablets". The purpose of the present investigation is to formulate a novel gastro retentive system, floating tablets of Sitagliptin Phosphate, an anti diabetic agent by direct compression technique using lactose as diluent. The drug-excipients interaction was ruled out through FTIR studies. Nine formulations of Sitagliptin Phosphate tablets were prepared using HPMC K100 and HPMC K4M as release retarding agents in different concentrations of 10, 15 and 20% w/w. The prepared batches were evaluated for organoleptic properties, hardness, friability, weight variation and *in vitro* drug release. All the formulations showed low

weight variation with rapid dispersion time and rapid *in vitro* dissolution.

15. **Pani *et al.,*** studied on "Formulation, development, and optimization of immediate release nateglinide tablets by factorial design". In the present study, selection of superdisintegrants among sodium starch glycolate, cross povidone, Starch-1500 and cross carmellose sodium (CCS) was carried out for development of immediate release nateglinide tablets (NTG). The results revealed that CCS was the best superdisintegrant for the development of immediate release tablets of NTG. The sign of the coefficient of the polynomial equation signified that the disintegration time was decreased and DR0.5h was increased by decreasing the hardness of the tablets as well as by increasing the concentration of CCS in the tablets. A checkpoint batch of the tablets was prepared by changing the value of independent variables within the range used in the preparation of factorial batches of tablets to check the validity of the evolved optimized mathematical model.
16. **Dahiya *et al.,*** studied the "Formulation and Evaluation of Granisetron Hydrochloride Orodispersible Tablets". The object of the present work was to formulate and evaluate orodispersible tablets of granisetronm hydrochloride, a highly water soluble, tasteless, antiemetic drug employing superdisintegrants explotab, crospovidone, Ac-Di-Sol. The mix powder blends of varying compositions were prepared and evaluated for micromeritic properties and then subjected to tablet preparation by direct compression method. The prepared tablets were evaluated for physical parameters, wetting time, disintegration time, content uniformity and *in vitro* dissolution. The physical parameters were found satisfactory and the disintegration time of tablets was found between 19 to 35 seconds which is well below the limit of disintegration time by European Pharmacopoeia.

17. **Ponugoti *et al.,*** described on "Formulation and Evaluation of Mouth Dissolving Tablets of Tramadol Hydrochloride". Tramadol HCl MDT were prepared by direct compression using Pharmaburst as coprocessed excipient and compared with a reference product (Rybix ODT, 50 mg). Physicochemical parameters including hardness, friability, weight variation, disintegration time and dissolution studies were determined for all the formulations. In-vivo studies were performed for the optimized formulation (F13), using as reference, a commercial product (Trambax IR, 50 mg), by a two-way crossover design under fasting conditions on eight healthy adult human subjects. Drug-plasma concentrations obtained from the bioequivalence study for test and reference products were analyzed in each subject by high performance liquid chromatography (HPLC), and basic pharmacokinetic parameters, including Cmax, Tmax, AUC0-t, AUC0-∞, t½ and λz, were calculated.T he tablet formulation prepared with Pharmaburst (F13) showed good flow properties, low disintegration time (15 s) and improved drug release (99 % at 30 min) compared with those of the reference product (88 % at 30 min) and passed 6 months accelerated stability test. Bioequivalence of the test product with that of the reference product under fasting conditions was established by computing 90 % confidence interval for the In-transformed pharmacokinetic parameters of Cmax, AUC0-t and AUC0-∞ for tramadol.
18. **Harita *et al.,*** studied the "A Short review on Mouth dissolving tablet". The main aim of floating drug delivery system is to develop a new dosage form which is convenient in administration and manufacturing, should free from side effects and should exhibit immediate release with better patient compliance and enhanced bioavailability. Tablets are the most widely accepted dosage forms in oral drug delivery system due to its numerous advantages. But beside the advantages there a few disadvantages like sudden

exposure of allergies, mental disability, motion sickness, unconsciousness, lack of water etc. In order to overcome such difficulties new drug delivery systems like fast dissolving tablets were developed.

19. **Shravani *et al.,*** studied the "Formulation and Evaluation of Fast Dissolving tablets of Montelukast sodium using Co-Processed Superdisintegrants". In the present work, fast dissolving tablets of Montelukast Sodium were prepared using novel coprocessed superdisintegrants consisting of crospovidone along with croscarmellose sodium, and crospovidone along with sodium starch glycolate in the different ratios (1:1, 1:2 and 1:3). Effect of co-processed superdisintegrants on wetting time, disintegrating time, drug content, and in-vitro release have been studied. The prepared tablets formulations were evaluated for post-compressional parameters. All the postcompressional parameter are evaluated were prescribed limits and results were within IP acceptable limits. The in-vitro disintegration time of fast dissolving tablets were found to be 12.06 to 39.14 sec. which is in the range of fulfilling the official requirements. The tablet shows the t50% and t90%between 0.94 min to 1.82 min and 3.61 min to 5.83 min respectively. Among all formulations CP3 showed 99.79% drug release within 4 min. It can be concluded from the present work that co-processed superdisintegrants of crosscarmellose sodium + crospovidone are superior to crospovidone + sodium starch glycolate co-processed superdisintegrants used in Montelukast Sodium fast dissolving tablets.
20. **PATEL *et al.,*** studied on "Formulation and Evaluation of Mouth Dissolving Tablets of Cinnarizine". The purpose of this research was to develop mouth dissolve tablets of cinnarizine by effervescent, superdisintegrant addition and sublimation methods. All the three formulations were evaluated for disintegration time, hardness and

friability, among these superdisintegrant addition method showed lowest disintegration time; hence it was selected for further studies. Further nine batches (B1-B9) were prepared by using crospovidone, croscarmellose sodium and L-HPC in different concentrations such as 5, 7.5 and 10%. All the formulations were evaluated for weight variation, hardness, friability, drug content, *in vitro* disintegration time, wetting time, *in vitro* dissolution. Formulation with 10% L-HPC showed the less disintegration time (25.3 s) and less wetting time (29.1 s). *In vitro* dissolution studies showed total drug release at the end of 6 min.

21. **Khanna *et al.,*** reviewed on "Fast Dissolving Tablets- A Novel Approach". In the present scientific scenario the drug delivery technology has become highly competitive and rapidly evolving with ever increasing demand. Fast dissolving tablet (FDT) is one such type of an innovative and unique drug delivery system which is swiftly gaining much attention in the research field of rapid dissolving technology. Oral route is the most expedient and safest route of drug delivery because of wide range of drugs are administered through this route. Recently researchers have developed fast dissolving tablet (FDT) which dissolve or disintegrate rapidly in mouth saliva without intake of water. When compared with conventional dosage form FDT can be a useful alternative as well.
22. **Saroha *et al.,*** studied the "Mouth dissolving tablets: An overview on future compaction in oral formulation technologies". This article reviews the earlier applications and methodologies of taste masking and also emphasize on the recent developments and approaches of bitterness reduction for orally used pharmaceuticals. Apart from the conventional methods of fabrication, this review also provides the detailed concept of some unique patents; technologies developed and marketed formulations of Mouth Dissolving Tablets (MDTs).

CHAPTER 3

AIM AND OBJECTIVE

3. AIM AND OBJECTIVES

- The present study is planned to develop Lercanidipine Hydrochloride into immediate release tablets by direct compression Method.
- Lercanidipine Hydrochloride, Lercanidipine, a dihydropyridine calcium-channel blocker, is used alone or with an angiotensin-converting enzyme inhibitor, to treat hypertension, chronic stable angina pectoris, and Prinzmetal's variant angina.
- Lercanidipine Hydrochloride have biological half-life of 8-10 hours and duration of action upto ≥ 24 hours.
- Lercanidipine Hydrochloride oral bioavailability is less than 10% due to its first pass metabolism.
- Lercanidipine Hydrochloride came under BCS class II having poor solubility and high permeability.
- The above said properties/characteristics which make Lercanidipine Hydrochloride suitable candidate for oral dissolving or mouth dissolving tablets.
- In this study, we tried to prepare Lercanidipine Hydrochloride MDT by using various types of disintegrants by direct compression method.

CHAPTER 4

PLAN OF WORK

4. PLAN OF WORK

- Literature survey.
- Procurement of drug, polymer and other excipients.
- Preformulation Studies
    - Solubility
    - Drug and excipient compatibility studies by FTIR
    - Bulk density
    - True density
    - Melting point determination
    - Carr's index
    - Hausner's ratio
    - Angle of repose
- Formulation development
- Evaluation Studies
    - Weight variation
    - Hardness
    - Friability
    - Thickness
    - Disintegration time
    - Content uniformity
    - Wetting time and water absorption ratio
    - *Invitro* Dissolution study
    - Stability Studies

CHAPTER 5

DISEASE PROFILE

5. DISEASE PROFILE

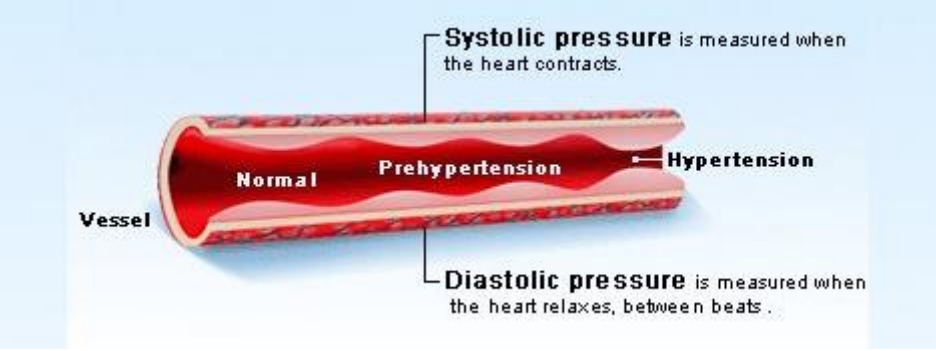
5.1. HYPERTENSION

Hypertension also known as high blood pressure or arterial hypertension, is a chronic medical condition in which the blood pressure in the arteries is elevated. Blood pressure is expressed by two measurements, the systolic and diastolic pressures, which are the maximum and minimum pressures, respectively, in the arterial system. The systolic pressure occurs when the left ventricle is most contracted, the diastolic pressure occurs when the left ventricle is most relaxed prior to the next contraction. Normal blood pressure at rest is within the range of 100–140 mmHg systolic and 60–90 mmHg diastolic. Hypertension is present if the blood pressure is persistently at or above 140/90 millimeters mercury (mmHg) for most adults; different criteria apply to children.

Table.No.3: Blood Pressure normal and Hypertension

Classification	Systolic pressure	Diastolic pressure
	mmHg	mmHg
Normal	90–119	60–79
High normal or pre-hypertension	120–139	80–89
Stage 1 hypertension	140–159	90–99
Stage 2 hypertension	≥160	≥100
Isolated systolic hypertension	≥140	<90

Fig. No.3 : Difference between Normal and Hypertension.



5.1.1.Risk factors

A number of risk factors increase the chances of having hypertension.

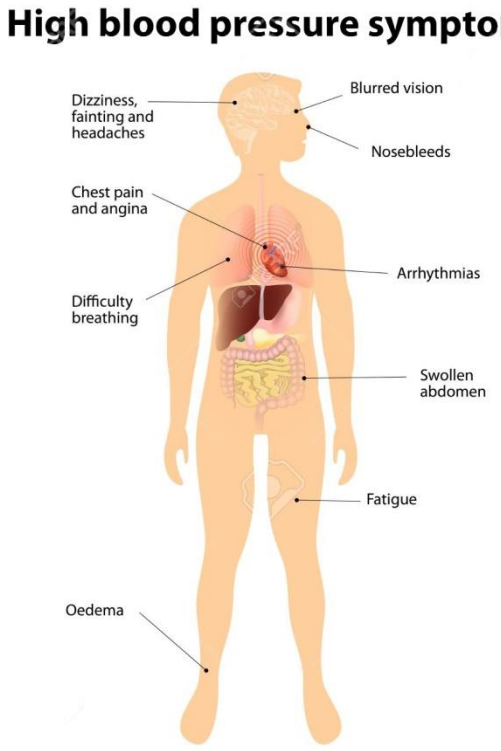
- **Age**: Hypertension is more common in people aged over 60 years. With age, blood pressure can increase steadily as the arteries become stiffer and narrower due to plaque build-up.
- **Ethnicity**: Some ethnic groups are more prone to hypertension.
- **Size and weight**: Being overweight or obese is a key risk factor.
- **Sex**: The lifetime risk is the same for males and females, but men are more prone to hypertension at a younger age. The prevalence tends to be higher in older women.
- **Existing health conditions**: Cardiovascular disease, diabetes, chronic kidney disease, and high cholesterol levels can lead to hypertension, especially as people get older.
- **Too much salt (sodium) in diet.** Too much sodium in diet can cause body to retain fluid, which increases blood pressure.
- **Too little potassium in diet.** Potassium helps balance the amount of sodium in cells. If don't get enough potassium in diet or retain enough potassium, it may accumulate too much sodium in blood.
- **Too little vitamin D in diet.** It's uncertain if having too little vitamin D in diet can lead to high blood pressure. Vitamin D may affect an enzyme produced by kidneys that affects blood pressure.
- **Drinking too much alcohol.** Over time, heavy drinking can damage heart.
- **Stress.** High levels of stress can lead to a temporary increase in blood pressure.
- **Not being physically active.** People who are inactive tend to have higher heart rates. The higher heart rate, the harder heart must work with each contraction and the stronger the force on arteries.

- **Using tobacco.** chewing tobacco immediately raise blood pressure temporarily, but the chemicals in tobacco can damage the lining of artery walls.
- **Certain chronic conditions.** Certain chronic conditions also may increase risk of high blood pressure, such as kidney disease, diabetes and sleep apnea.

5.1.2.Symptoms of severe hypertension can include:

Headaches, Shortness of Breath, Nosebleeds, Flushing, Dizziness, Chest Pain, Visual Changes, Blood In The Urine, These symptoms require immediate medical attention.

Fig. No.4 : Hypertension Symptoms.

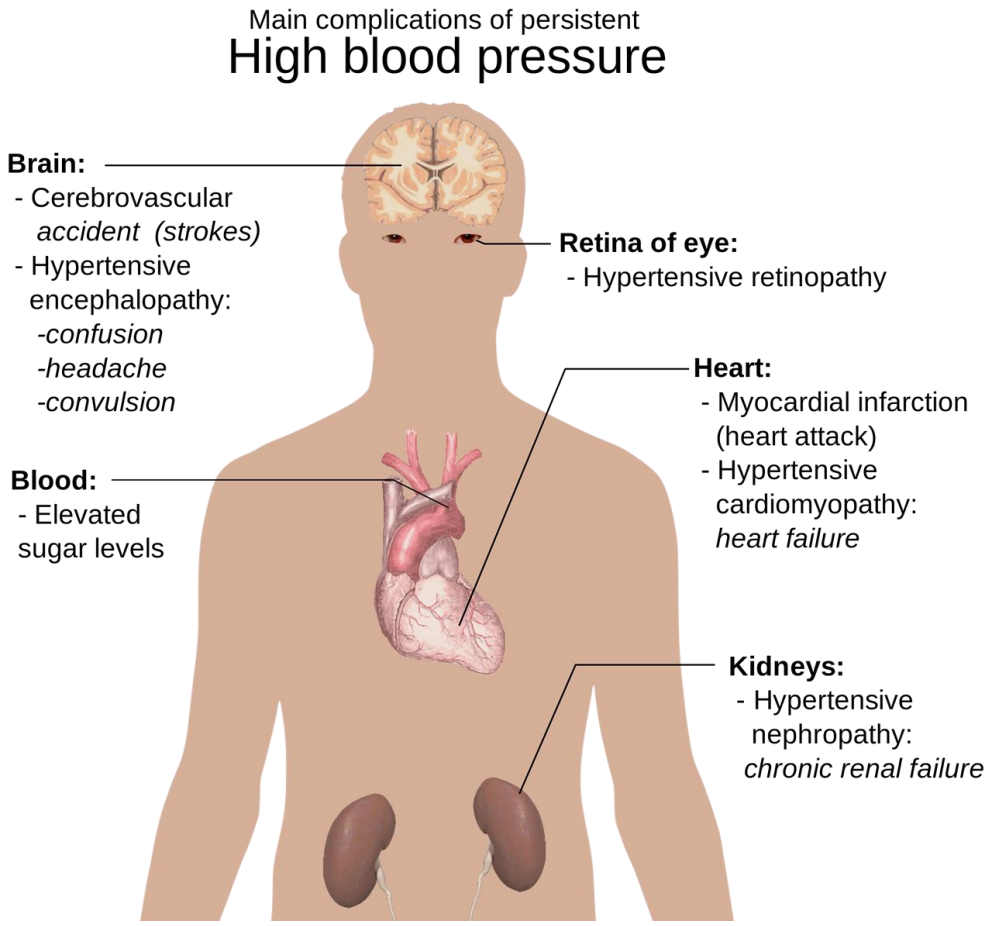


5.1.3.Pathophysiology

Hypertension is a chronic elevation of blood pressure that, in the long-term, causes end-organ damage and results in increased morbidity and mortality. Blood pressure is the product of cardiac output and systemic vascular resistance. It follows that patients with arterial hypertension may have an increase in cardiac output, an increase in systemic vascular resistance, or both. In the younger age group, the cardiac output is often elevated, while in older patients

increased systemic vascular resistance and increased stiffness of the vasculature play a dominant role. Vascular tone may be elevated because of increased α-adrenoceptor stimulation or increased release of peptides such as angiotensin or endothelins. The final pathway is an increase in cytosolic calcium in vascular smooth muscle causing vasoconstriction. Several growth factors, including angiotensin and endothelins, cause an increase in vascular smooth muscle mass termed vascular remodelling. Both an increase in systemic vascular resistance and an increase in vascular stiffness augment the load imposed on the left ventricle, this induces left ventricular hypertrophy and left ventricular diastolic dysfunction.

Fig. No.5 : Main Complications of Hypertension.



5.1.4.Treatment

The ultimate goal in treatment of the hypertensive patient is to achieve the maximum reduction in the long-term total risk of cardiovascular morbidity and mortality. This requires:

- Treatment of all reversible risk factors identified including smoking, dyslipidaemia and diabetes mellitus,
- Appropriate management of associated clinical conditions such as congestive heart failure, coronary artery disease, peripheral vascular disease and transient ischaemic attacks,
- Achieving office blood pressure values <130/80 mmHg for patients with diabetes mellitus or chronic renal disease. When home or ambulatory pressure measurements are used to evaluate the efficacy of treatment, daytime values around 10–15 mmHg lower for systolic blood pressure and 5–10 mmHg lower for diastolic blood pressure are the goal values.

Treating systolic and diastolic blood pressure to target is associated with a decrease in cardiovascular complications. This includes 35%–40% mean reduction in stroke incidence, 20%–25% mean reduction in myocardial infarction and >50% mean reduction in heart failure.

There are several strategies for achieving therapeutic goals: lifestyle modifications, pharmacological modifications and general strategies for hypertensive therapy.

5.1.5.Lifestyle changes to treat high blood pressure

- Eating a healthier diet with less salt (the Dietary Approaches to Stop Hypertension, or DASH, diet)
- Exercising regularly
- Quitting smoking
- Limiting the amount of alcohol drink
- Maintaining a healthy weight or losing weight if overweight or obese.

5.1.6.Medications

People with blood pressure higher than 130 over 80 may use medication to treat hypertension. Drugs are usually started one at a time at a low dose. Side effects associated with antihypertensive drugs are usually minor. Eventually, a combination of at least two antihypertensive drugs is usually required.

A range of drug types are available to help lower blood pressure, including

- **ACE inhibitors** – such as enalapril, lisinopril, perindopril and ramipril
- **Angiotensin-2 receptor blockers (ARBs)** – such as candesartan, irbesartan, losartan, valsartan and olmesartan
- **Calcium channel blockers** – such as amlodipine, felodipine and nifedipine or diltiazem and verapamil.
- **Diuretics** – such as indapamide and bendroflumethiazide
- **Beta-blockers** – such as atenolol and bisoprolol
- **aApha-blockers** – such as doxazosin
- **Renin inhibitors** – such as aliskiren
- **Other diuretics** – such as amiloride and spironolactone

5.1.7.Alternative medicine

Although diet and exercise are the most appropriate tactics to lower blood pressure, some supplements also may help lower it. These include:

- Fiber, such as blond psyllium and wheat bran, Minerals, such as magnesium, calcium and potassium, Folic acid, Supplements or products that increase nitric oxide or widen blood vessels (vasodilators), such as cocoa, coenzyme Q10, L-arginine or garlic, Omega-3 fatty acids, found in fatty fish, fish oil supplements or flaxseed.

5.2.1. Angina Pectoris:

Angina a symptom of an underlying heart condition. It means that the heart is not getting enough blood and as a result, not enough oxygen. This decrease of oxygen being delivered to the muscle of the heart happens if one or more coronary arteries are narrowed or blocked, a condition called atherosclerosis. This type of blockage may result in chest pain. And while angina does not usually damage the heart, and the pain might only last a few minutes, it is a warning sign that should not ignore.

5.2.2.Different types of angina

Five different kinds of angina have been identified, with the two most common being **stable angina** and **unstable angina**.

Stable angina occurs when the heart has to work harder than normal, during exercise, for example. It has a regular pattern, and if already know that patient have stable angina, it will be able to predict the pattern. Once stop exercising, or take medication (usually nitroglycerin) the pain goes away, usually within a few minutes.

Unstable angina is more serious, and may be a sign that a heart attack could happen soon. There is no predictable pattern to this kind of angina, it can just as easily occur during exercise as it can while are resting. It should always be treated as an emergency. People with unstable angina are at increased risk for heart attacks, cardiac arrest, or severe cardiac arrhythmias (irregular heartbeat or abnormal heart rhythm). Less common kinds of angina include:

- Variant angina
- Microvascular angina
- Atypical angina

Variant angina is also known as **Prinzmetal's angina**. It often occurs while someone is resting (usually between midnight and 8:00 in the morning), and it has no predictable pattern—that is, it is not brought on by exercise or emotion. This kind of angina may cause severe pain, and is usually the result of a spasm in a coronary artery.

Microvascular angina—sometimes referred to as Syndrome X—occurs when tiny vessels in the heart become narrow and stop functioning properly, even if the bigger arteries are not blocked by plaque. Usually it is treated with common angina medications

Atypical angina often doesn't cause pain, but may feel a vague discomfort in chest, experience shortness of breath, feel tired or nauseous, have indigestion, or pain in back or neck. Women are more likely than men to have feelings of vague chest discomfort.

Causes:

High blood pressure (for more on high blood pressure, Diabetes, Unhealthy cholesterol levels, Smoking, Lack of exercise, Obesity, Too much salt in diet, Excessive use of alcohol, Family history of CAD or stroke, Being male, Being a postmenopausal woman, Age.

5.2.3.Classification of Drugs

1. Organic Nitrates and Nitrites

Nitroglycerin, Isosorbide Dinitrate, Isosorbide mononitrate, Amyl nitrite.

2. Calcium Channel Blockers

a) **Dihydropyridines:** Amlodipine, Nicardipine, Nifedipine, Nimodipine, **Lercanidipine,** Nisoldipine, Nitrendipine.

b) **Miscellaneous Drugs:** Verapamil, Diltiazem, Bepridil.

3. Beta-Adrenoceptor Blockers

Beta 1 and Beta 2 Antagonist: Propranolol, Penbutolol, Pindolol, Satolol, Timolol.

Beta 1 Selective Blockers: Metoprolol, Atenolol, Esmolol, Acebutolol, Betaxolol.

CHAPTER 6

DRUG PROFILE

6. DRUG PROFILE- LERCANIDIPINE HYDROCHLORIDE

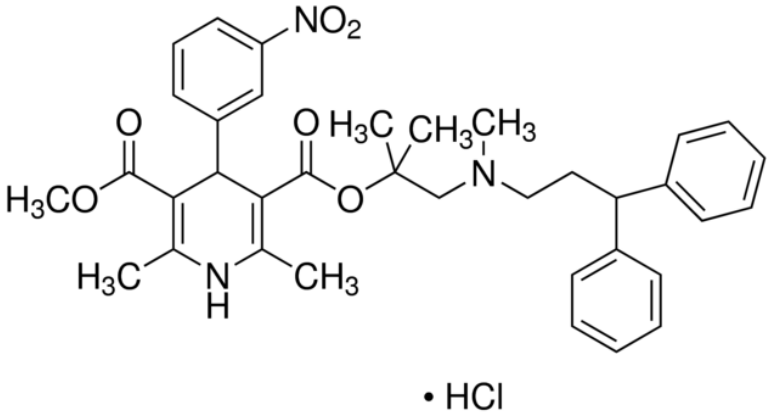
6.1. Description

Lercanidipine Hydrochloride is an antihypertensive (blood pressure lowering) drug. It belongs to the structurally related to the 1,4-dihydropyridines class of calcium channel blockers, is used alone or with an angiotensin-converting enzyme inhibitor, to treat hypertension, chronic stable angina pectoris, and Prinzmetal's variant angina.

Lercanidipine Hydrochloride which work by relaxing and opening the blood vessels allowing the blood to circulate more freely around the body. This lowers the blood pressure and allows the heart to work more efficiently.

Lercanidipine Hydrochloride isslightly yellow crystalline powder and melts at 197 to 201 °C (387 to 394 °F) in crystal form I and 207 to 211 °C (405 to 412 °F) in crystal form II. It is readily soluble in chloroform and methanol, but practically insoluble in water. This high lipophilicity (compared to older dihydropyridines) is intentional because it causes the substance to bind to lipid membranes, allowing for a longer duration of action.

Fig.No.6: Chemical Structure of Lercanidipine Hydrochloride



6.2. CHEMICAL DATA

- Empirical formula - $C_{36}H_{41}N_3O_6$
- Molecular weight - 611.739 g/mol

- CAS Registry No. - 100427-26-7

6.2.1. Systemic (IUPAC) Name:

5-O-[1-[3,3-diphenylpropyl(methyl)amino]-2-methylpropan-2-yl] 3-O-methyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate

6.3. Pharmacology:

6.3.1 Indication

For the treatment of Hypertension, management of angina pectoris and Raynaud's syndrome.

6.3.2. Pharmacodynamics

Lercanidipine, a dihydropyridine calcium-channel blocker, is used alone or with an angiotensin-converting enzyme inhibitor, to treat hypertension, chronic stable angina pectoris, and Prinzmetal's variant angina. Lercanidipine is similar to other peripheral vasodilators. Lercanidipine inhibits the influx of extra cellular calcium across the myocardial and vascular smooth muscle cell membranes possibly by deforming the channel, inhibiting ion-control gating mechanisms, and/or interfering with the release of calcium from the sarcoplasmic reticulum. The decrease in intracellular calcium inhibits the contractile processes of the myocardial smooth muscle cells, causing dilation of the coronary and systemic arteries, increased oxygen delivery to the myocardial tissue, decreased total peripheral resistance, decreased systemic blood pressure, and decreased afterload.

6.3.3. Mechanism of action

By deforming the channel, inhibiting ion-control gating mechanisms, and/or interfering with the release of calcium from the sarcoplasmic reticulum, Lercanidipine inhibits the influx of extracellular calcium across the myocardial and vascular smooth muscle cell membranes. The decrease in intracellular calcium inhibits the contractile processes of the myocardial smooth muscle cells, causing dilation of the coronary and systemic arteries, increased oxygen delivery to the myocardial tissue,

decreased total peripheral resistance, decreased systemic blood pressure, and decreased afterload.

6.3.4. Pharmacokinetic Parameters:

Absorption

The absorption from the gastrointestinal tract was rapid, with T max ranging from 0.75 to 1.5.

Distribution

The apparent volume of distribution for lercanidipine was in the range of 2-2.5 L/kg.

Metabolism

When orally administered, lercanidipine HCl undergoes extensive biotransformation, and practically no unchanged drug is present in urine and feces. The metabolism of lercanidipine involves aromatization of the heterocyclic ring, oxidative loss of the N side-chain, and its glucuronidation. Other pathways involved include nitro reduction, *N,N*-didealkylation, and glucuronidation. Aromatization of the heterocyclic ring and hydroxylation of the side-chain, with consequential loss of *N* - methyl -*N*- (3,3 - diphenyl) propylamine groups, produce a primary alcohol, metabolite M8, which undergoes subsequent glucuronidation to metabolite M4. Nitro reduction with *N,N*-didealky-lation leads to the formation of an amine metabolite M5. Another metabolite, M7, was structurally closely related to M8 but could not be characterized because it was present in very small amounts. M7 was conjugated with glucuronic acid to produce M5.

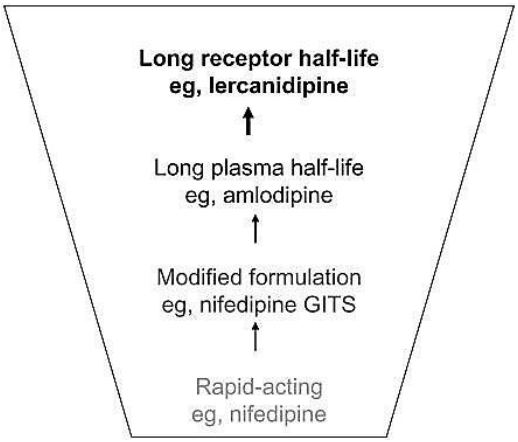
Excretion

The 93.4 to 96.1% of the administered drug was excreted about 43.8% in the urine and 50.4% in the feces. No unchanged drug was detected in the urine, demonstrating an effectively complete biotransformation of lercanidipine before excretion.

- Bio-availability ~10%
- Half life – 8-10 hours

- Duration of Action ≥ 24 Hours
- Protein binding - > 98%

Fig.No.7: Evolution of dihydropyridine calcium antagonists for improved clinical efficacy and tolerability. Abbreviations: GITS, gastrointestinal therapeutic system.



6.3.5.Contraindications

Like other dihydropyridines, lercanidipine is contraindicated in unstable angina pectoris, uncontrolled cardiac failure, shortly after a myocardial infarction, and in patients with left ventricular outflow tract obstruction. It is also contraindicated during pregnancy and in women who may become pregnant, because data regarding safety for the unborn are lacking, as well as in patients with severe liver and renal impairment.

The drug must not be combined with strong inhibitors of the liver enzyme CYP3A4 or with the immunosuppressant drug ciclosporin.

6.3.6.Overdose

Overdosing of up to 80 times the usual therapeutic dose has been described. Expected symptoms include severe hypotension (low blood pressure) and reflex tachycardia. Bradycardia (slow heartbeat) can also occur due to blockage of calcium channels in the atrioventricular node of the heart. There is no treatment besides monitoring blood pressure and heart function. Dialysis is likely ineffective because most of the

lercanidipine is bound to blood plasma proteins and lipid membranes of cells.

6.3.7.Interactions

The substance is metabolised by the liver enzyme CYP3A4. In a study, the strong CYP3A4 inhibitor ketoconazole increased the maximal blood plasma concentrations of lercanidipine by a factor of eight, and the area under the curve by a factor of 15. In another study, ciclosporin increased lercanidipine plasma levels threefold when given at the same time. Other inhibitors of this enzyme, such as itraconazole, erythromycin, and grapefruit juice, are also expected to increase plasma concentrations and thus amplify the antihypertensive effect.

Conversely, CYP3A4 inductors such as carbamazepine, rifampicin, and St John's wort probably lower plasma levels and effectiveness of lercanidipine. By comparison, amlodipine has a lower potential for CYP3A4 mediated interactions.

Lercanidipine increases plasma levels of ciclosporin and digoxin.

6.3.8.Side Effects

Headache, Dizziness, Ankle swelling, Faster heart beat, Awareness of the beating or your heart (palpitations), Redness of the face and neck, Sleepiness, Feeling and being sick, Rash, Muscle pain, Passing large amounts of urine (water) and passing urine more frequently, Tiredness, Fainting, Light-headedness, Indigestion, Diarrhoea, Angina (chest pain), Pain in the stomach, Allergic reactions, Swelling of the gums, Changes to the way the liver functions, Low blood pressure

6.3.9.Serious Allergic Reaction:

- getting a skin rash that may include itchy, red, swollen, blistered or peeling skin
- wheezing
- tightness in the chest or throat
- having trouble breathing or talking
- swelling of the mouth, face, lips, tongue, or throat.

7. EXCIPIENTS PROFILE

7.1. Crospovidone

Nonproprietary Names

BP: Crospovidone

PhEur: Crospovidone

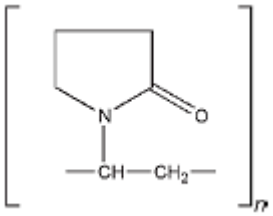
USP-NF: Crospovidone

Synonyms: Crospovidonum, crosslinked povidone, Kollidon CL, PolyplasdoneXL-10, polyvinylpolypyrrolidone, PVPP, 1-vinyl-2-pyrrolidinone homopolymer.

Chemical Name and CAS Registry Number: 1-Ethenyl-2-pyrrolidinone homopolymer [9003-39-8]

Empirical Formula and Molecular Weight:

(C_6H_9NO) >1 000 000



Structural Formula

Functional Category

Tablet disintegrant.

Description

Crospovidone is a white to creamy-white, finely divided, free-flowing, practically tasteless, odorless or nearly odorless, hygroscopic powder.

Solubility:

Practically insoluble in water and most common organic solvents.

Applications in Pharmaceutical Formulation or Technology

- Crospovidone is a water-insoluble tablet disintegrant and dissolution agent used at 2–5% concentration in tablets prepared by direct compression or wet- and dry-granulation methods.
- It rapidly exhibits high capillary activity and pronounced hydration capacity, with little tendency to form gels.
- Larger particles provide a faster disintegration than smaller particles.
- Crospovidone can also be used as a solubility enhancer.
- The drug is adsorbed on to crospovidone in the presence of a suitable solvent and the solvent is then evaporated. This technique results in faster dissolution rate.

CHAPTER 7

EXCIPIENT PROFILE

7.2. Croscarmellose Sodium

Nonproprietary Names

BP: Croscarmellose Sodium

JP: Croscarmellose Sodium

PhEur: Croscarmellose Sodium

USP-NF: Croscarmellose Sodium

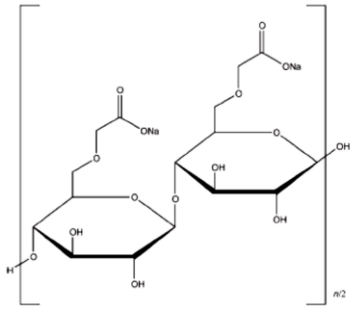
Synonyms: Ac-Di-Sol, crosslinked carboxy methyl cellulose sodium, Explocel, modified cellulose gum, Nymcel, ZSX Pharmacel XL, Primellose, Solutab, Vivasol.

Chemical Name and CAS Registry Number:

Cellulose, carboxymethyl ether, sodium salt, crosslinked [74811-65-7]

Empirical Formula and Molecular Weight :

The USP 32 describes carboxymethylcellulose sodium as the sodium salt of a polycarboxymethyl ether of cellulose.



Structural Formula

Functional Category: Tablet and capsule disintegrant.

Description: Croscarmellose sodium occurs as an odorless, white or grayish white powder.

Solubility

Insoluble in water, croscarmellose sodium rapidly swells to 4–8 times its original volume on contact with water. Practically insoluble in acetone, ethanol and toluene.

Applications in Pharmaceutical Formulation or Technology

- Croscarmellose sodium is used in oral pharmaceutical formulations as a disintegrant for capsules, tablets, and granules.
- In tablet formulations, croscarmellose sodium may be used in both direct-compression and wet-granulation processes.
- Croscarmellose sodium at concentrations up to 5% w/w may be used as a tablet disintegrant, although normally 2% w/w is used in tablets prepared by direct compression and 3% w/w in tablets prepared by a wet-granulation process.

7.3. Sodium Starch Glycolate

Nonproprietary Names

BP: Sodium Starch Glycolate

PhEur: Sodium Starch Glycolate

USP-NF: Sodium Starch Glycolate

Synonyms: Carboxymethyl starch, sodium salt, carboxymethylamylum natricum, Explosol, Explotab, starch carboxymethyl ether, sodium salt, Tablo,Vivastar P.

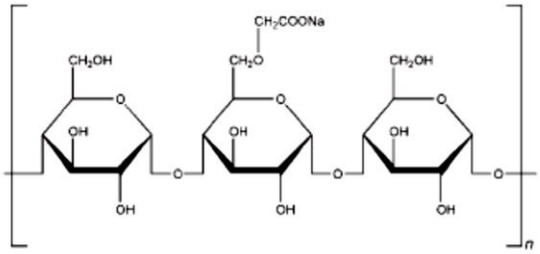
Chemical Name and CAS Registry Number:

Sodium carboxymethyl starch [9063-38-1]

Empirical Formula and Molecular Weight :

The molecular weight is typically $5X10^5$–110^6.

Structural Formula



Functional Category: Tablet and capsule disintegrant.

Description: Sodium starch glycolate is a white or almost white free-flowing very hygroscopic powder. When examined under a microscope it is seen to consist of granules, irregularly shaped, ovoid or pear-shaped, 30–100 mm in size, or rounded, 10–35 mm in size, compound granules consisting of 2–4 components occur occasionally. The granules show considerable swelling in contact with water.

Solubility

In water, sodium starch glycolate swells to up to 300 times its volume.

Applications in Pharmaceutical Formulation or Technology

- Sodium starch glycolate is widely used in oral pharmaceuticals as a disintegrant in capsuleand tablet formulations.
- It is commonly used in tablets prepared by either direct-compression or wet-granulation processes.

- The usual concentration employed in a formulation is between 2% and 8%, with the optimum concentration about 4%, although in many cases 2% is sufficient.
- Disintegration occurs by rapid uptake of water followed by rapid and enormous swelling. Although the effectiveness of many disintegrants is affected by the presence of hydrophobic excipients such as lubricants.

7.4. Starch 1500

Nonproprietary Names

BP, JP, PhEur, USP : starch

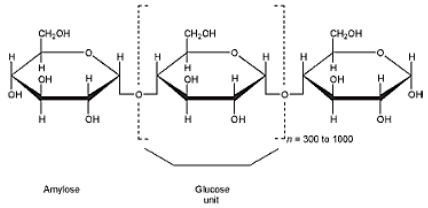
Synonyms: partially pregelatinized maize starch.

Chemical Name and CAS Registry Number:

Starch [9005-25-8]

Empirical Formula and Molecular Weight: $(C_6H_{10}O_5)n$ where n = 300–1000.

Structural Formula



Functional Category

Tablet and capsule diluent, tablet and capsule disintegrant, tablet Binder, thickening agent.

Description

Starch 1500 co-processed starch excipient is a mix of globally accepted excipients (corn starch and pregelatinized starch) designed for use in capsules and tablets.

Applications in Pharmaceutical Formulation or Technology

- Starch 1500 is a unique pharmaceutical excipient combining several properties in a single product act as a binder, disintegrant, filler and flow-aid while having lubricant properties.
- Starch 1500 cuts process and material costs by reducing or eliminating polymeric binders, superdisintegrants, high levels of lubricants and glidants and manufacturing steps.

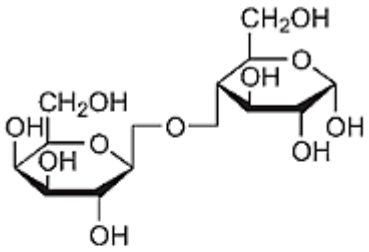
7.5. Lactose

Nonproprietary Names

BP : Anhydrous Lactose
JP : Anhydrous Lactose
PhEur : Anhydrous Lactose
USP : Anhydrous Lactose

Synonyms: Anhydrous 60M, Anhydrous Direct Tableting (DT), Lactopress Anhydrous, Lactopress Anhydrous 250, SuperTab 22AN, saccharum lactis.

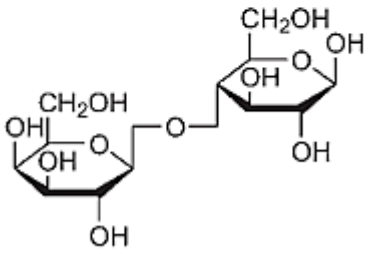
Chemical Name and CAS Registry Number:
O-bD-Galactopyranosyl-(1!4)-b-D-glucopyranose [63-42-3]



Anhydrous α-lactose

Empirical Formula and Molecular Weight:
$C_{12}H_{22}O_{11}$ 342.30

Structural Formula



Anhydrous β-lactose

Functional Category

Directly compressible tablet excipient, dry powder inhaler carrier, lyophilization aid, tablet and capsule diluent, tablet and capsule filler.

Description

Anhydrous lactose occurs as white to off-white crystalline particles or powder. Several different brands of anhydrous lactose are commercially available which contain anhydrous β-lactose and anhydrous α lactose. Anhydrous lactose typically contains 70–80% anhydrous b-lactose and 20–30% anhydrous a-lactose.

Applications in Pharmaceutical Formulation or Technology

- Anhydrous lactose is widely used in direct compression tableting applications, and as a tablet and capsule filler and binder.
- Anhydrous lactose can be used with moisture-sensitive drugs due to its low moisture content. It may also be used in intravenous injections.

7.6. Mannitol

Nonproprietary Names

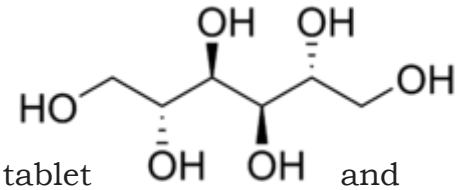
BP : Mannitol
JP : D-Mannitol
PhEur : Mannitol
USP : Mannitol

Synonyms: Cordycepic acid, C Pharm Mannidex, E421, Emprove, manna sugar.

Chemical Name and CAS Registry Number: D-Mannitol [69-65-8]

Empirical Formula and Molecular Weight: $C_6H_{14}O_6$ and 182.17

Structural Formula



Functional Category

Diluent, plasticizer, sweetening agent, tablet and capsule diluents, therapeutic agent, tonicity agent.

Description

Mannitol is D-mannitol. It is a hexahydric alcohol related to mannose and isomeric with sorbitol. Mannitol occurs as a white, odorless, crystalline powder, or free flowing granules. It has a sweet taste, approximately as sweet as glucose and half as sweet as sucrose, and imparts a cooling sensation in the mouth. Microscopically, it appears as orthorhombic needles when crystallized from alcohol. Mannitol shows polymorphism.

Applications in Pharmaceutical Formulation or Technology

- Mannitol is widely used in pharmaceutical formulations and food products. In pharmaceutical preparations it is primarily used as a diluent (10–90% w/w) in tablet formulations.
- Mannitol may be used in direct-compression tablet applications for which the granular and spray-dried forms are available.
- Mannitol is commonly used as an excipient in the manufacture of chewable tablet.

- In lyophilized preparations, mannitol (20–90% w/w) has been included as a carrier to produce a stiff, homogeneous cake that improves the appearance of the lyophilized plug in a vial. A pyrogen-free form is available specifically for this use.
- Mannitol has also been used to prevent thickening in aqueous antacid suspensions of aluminum hydroxide (<7% w/v).

7.7. Magnesium Stearate

Nonproprietary Names

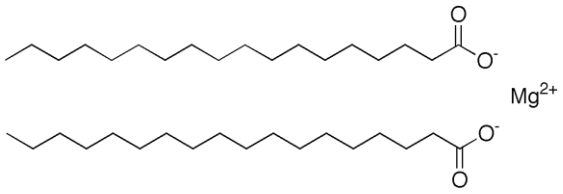
BP: Magnesium Stearate
JP: Magnesium Stearate
PhEur: Magnesium Stearate
USP-NF: Magnesium Stearate

Synonyms: Dibasic magnesium stearate, magnesium distearate, magnesia stearas.

Chemical Name and CAS Registry Number: Octa decanoic acid magnesium salt and [557-04-0]

Empirical Formula and Molecular Weight: $C_{36}H_{70}MgO_4$ and591.24

Structural Formula: $[CH_3(CH2)_{16}COO]_2Mg$



Functional Category: Tablet and capsule lubricant

Description

Magnesium stearate as a compound of magnesium with a mixture of solid organic acids that consists chiefly of variable proportions of magnesium stearate and magnesium palmitate. ($C_{32}H_{62}MgO_4$).

Magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of

stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.

Applications in Pharmaceutical Formulation or Technology

Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w. It is also used in barrier creams.

7.8. Aspartame

Nonproprietary Names

BP: Aspartame

PhEur: Aspartame

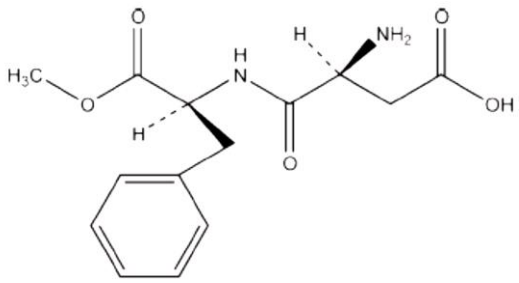
USP-NF: Aspartame

Synonyms: 3-amino-N-(a-methoxycarbonylphenethyl)-succinamic acid, APM, aspartamum, aspartyl phenylamine methyl ester, Canderel, E951, Equal, methyl N-L-a-aspartyl-L-phenylalaninate, NatraTaste, NutraSweet, Pal Sweet, Pal Sweet Diet.

Chemical Name and CAS Registry Number: N-L-a-Aspartyl-L-phenylalanine 1-methyl ester [22839-47-0]

Empirical Formula and Molecular Weight: C14H18N2O5 294.30

Structural Formula:



Functional Category: Sweetening agent.

Description: Aspartame occurs as an off white, almost odorless crystalline powder with an intensely sweet taste.

Applications in Pharmaceutical Formulation or Technology

Aspartame is used as an intense sweetening agent in beverage products, food products, and table-top sweeteners, and in pharmaceutical preparations including tablets, powder mixes, and vitamin preparations. The approximate sweetening power is 180–200 times that of sucrose.

Unlike some other intense sweeteners, aspartame is metabolized in the body and consequently has some nutritive value: 1 g provides approximately 17 kJ (4 kcal).

CHAPTER 8

MATERIALS AND EQUIPMENTS

8. MATERIALS AND EQUIPEMENTS

8.1. MATERIALS USED:

Table. No. 4: Materials Used

S.No	Materials	Suppliers / Manufacturer
1	Crosspovidone / PVP Disintegrant	Chemico Glass & Scientific Company, Erode.
2	Croscarmellose sodium (CCS)	Loba Chemie Pvt Ltd
3	Sodium Starch Glycolate (SSG)	Nice chemicals
4	Starch 1500	Nice chemicals
5	Lactose	Loba Chemie Pvt Ltd
6	Mannitol	Nice chemicals
7	Magnesium Stearate	Loba Chemie Pvt Ltd
8	Sucralose	Nice chemicals

8.2. INSTRUMENTS USED

Table. No. 5: Instruments Used

S.No	Equipment	Manufacturer
1	Digital Balance	Shimadzu Analytical
2	Sieves	Indicot (India)
3	Tapped Density Tester	Electrolab
4	Mechanical Stirrer	Remi Motors, Mumbai
5	UV-Visible Spectrophotometer	LAB INDIA UV 3000+
6	Dissolution Test Apparatus	Labindia Analytical Instruments Pvt Ltd. Mumbai , Model-DISSO 2000
7	Temperature controller(hot air oven)	ROLEX
8	FTIR	BRUKER HTS-XT
9	Compression machine	Proton Mini Press
10	Vernier Calipers	Indicot
11	Disintegration Test Apparatus,USP	ROLEX

CHAPTER 9

PREFORMULATION

9. PREFORMULATION

Preformulation testing is first step in the rational development of dosage forms of a drug substance. It can be defined as – "as investigation of physical and chemical properties of a drug substance alone and when combined with excipients". The overall objective of preformulation testing is to generate information useful to the formulation in developing stable and bioavailable dosage forms that can be mass produced. The preformulation should start at the point after biological screening, when a decision is made for further development of compound in clinical trials. The preformulationstudies should consider the following before going through the formal program which includes:

- Available physicochemical data (including chemical structure and different salts available).
- Anticipated dose
- Supply situation and development schedule.
- Availability of stability , assay.
- Nature of information the formulator should have or would like to have.

The following preformulation studies were performed for the obtained sample of drug.

9.1. Organoleptic properties

9.1.1. Color and nature

Transferred small quantity of the sample on a white piece of paper, spreaded the powder and examined visually.

Lercanidipine Hydrochloride is a white citrine-yellow crystalline powder.

9.1.2. Particle Size , Shape and Surface Area

Various physical and chemical properties of drug substances are affected by their particle size distribution and shapes. Size also plays a role inthe homogeneity of final tablet. When large differences in size

exist between the API and excipientsm mutual sieving (demixing) effects can occur making through mixing difficult on, it attained, difficult to maintain during the subsequent processing steps.

If the material become too fine, then undesirable properties such as electrostatin force effects and other surface active properties causing undue stickiness and lack of flowability manifest. It is probably safest to grind most drugs having particles that are approx 100μm in diameter.

Table. No. 6: General Techniques For Determining Particle Size

Techniques	Particle size(μm)
Microscopic	1-100
Sieve	>50
Sedimentation	>1
Eutriation	1-50
Centrifugal	<50
Permeability	>1
Light Scattering	0.5-50

9.2. Physical characteristics:

9.2.1.Flow properties:

The flow properties of powders are critical for an efficient tableting operation. A good flow of powder or granulation to be compressed is necessary to assure efficient missing and acceptable weight uniformity for the compressed tablets. If a drug is identified at the pre formulation stage to be “poorly flowable”, the problem can be solved by selecting appropriate excipients. In some cases, drug powders may have to be pre-compressed or granulated to improve their flow properties. During pre formulation evaluation of drug substance, therefore, its flowability characteristic should be studied, especially when the anticipated dose of the drug is large.

9.2.2.Angle of Repose:

Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane.

Procedure:

A funnel was kept vertically in a stand at a specified height above a graph paper placed on a horizontal surface. The funnel bottom is closed and 10 gm of sample powder is filled in funnel. Then funnel was opened to release the powder on the paper to form a smooth conical heap, is found by measuring in different direction. The height of the heap was measured by using scale. The values of angle of repose are calculated by using the following formula:

$$\tan\theta = h/r$$

$$\theta = \tan^{-1}(h/r)$$

Where, θ – angle of repose

h- Height of the heap

r - Radius of the heap

Table. No. 7: Angle of repose limits.

Angel of repose	Flowability
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

The results shown in results and discussion.

9.2.3.Bulk density

Bulk density is the ratio of mass of powder to the bulk volume. Bulk density largely depends on particle shape, as the particles become

more spherical in shape, bulk density is increase. In addition as granules size increase, bulk density decrease.

Bulk density is determined by measuring the volume of a known mass of powder sample that has been passed through a screen into a graduated cylinder.

Procedure:

A known quantity of powder was poured into the measuring cylinder carefully level the powder with out compacting, if necessary and read the unsettled apparent volume. Calculate the bulk density, in gm per ml, by the formula

$$(\rho_b) = m / V_b.$$

Where, ρ_b =Bulk Density

m = mass of powder

V_b = initial / bulk volume

The results shown in results and discussion

Tapped density:

Tapped density is the ratio of mass of powder to the tapped volume.

Procedure:

A quantity of 5g of the powder (W) from each formula was introduced into a 25 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 sec intervals. The tapping was continued until no further change in volume was noted. Calculate the tapped density, in gm per ml, by the formula:

$$(\rho_t) = m/V_t$$

Where, ρ_t =Tapped Density

m = mass of powder

V_t= final / tapped volume

9.2.4.Measurement of Powder Compressibility:

The compressibility Index are measures of the propensity of a powder to be compressed. As such, they are measures of the relative importance of inter particulate interactions. In a free flowing powder, such interactions are generally less and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater inter particle interactions, and a greater difference between bulk and tapped densities will be observed. These differences are reflected in the compressibility Index Calculated by the formula,

$$\% \text{ Compressibility (Carr's index)} = \frac{\text{Tapped density - Initial bulk density}}{\text{Tapped density}} \times 100$$

Table. No: 8. Flow properties and corresponding Carr's Index values

Excellent	<10
Good	11 – 15
Fair	16 – 20
Possible	21 – 25
Poor	26 – 31
Very poor	32 – 37
Very very poor	>38

The results are shown in results and discussion.

9.2.5.Hausner Ratio:

It is the ratio of volume of tapped volume or tapped density to bulk density. **Hausner Ratio = Vb/Vt or ρ_t / ρ_b.**

Table. No: 9. Flow Properties and Corresponding Hausner's ratio

Excellent	1.00 – 1.11
Good	1.1 – 1.18
Fair	1.19 – 1.25
Possible	1.26 -1.34
Very poor	1.35 -1.45
Very very poor	>1.60

9.2.6. Melting point:

It is one of the parameters to judge the purity of crude drugs. In case of pure chemicals, melting points are very sharp and constant.

Procedure:

A small quantity of powder was placed into a fusion tube. That tube is placed in the melting point apparatus containing castor oil. The temperature of the castor oil was gradual increased automatically and read the temperature at which powder started to melt and the temperature when all the powder gets melted. The results shown in results and discussion.

9.2.7. Solution properties:

Solubility:

A semi quantitative determination of the solubility was made by adding solvent in small incremental amount to a test tube containing fixed quantity of solute or vice versa. After each addition, the system is vigorously shaken and examined visually for any undissolved solute particles. The solubility are expressed in terms of ratio of solute and solvent. The results are shown in table.9.

9.2.8 Identification of drug and compatibility study:

9.2.8 a) Identification of drug By FT-IR:

The drug can be identified by using FT-IR.

9.2.8 b) By Physical observation

It was determined as per procedure given in method section. The following table illustrated the result.

Table. No:10. Physical Compatibility Studies

Test	Observations	Inference
Physical compatibility	No change of color	These materials are compatible for formulations.

9.2.8 c) Procedure By FT-IR Studies

The IR spectrums of the Lercanidipine Hydrochloride with exipients were taken by preparing dispersion in dry potassium bromide under dry condition. Superimposed these spectra. The transmission minima (absorption maxima) in the spectra obtained with the sample corresponded in position and relative size to those in the spectrum obtained with the standards.

9.3. UV SPECTROSCOPIC METHOD FOR ANALYSIS OF LERCANIDIPINE HYDROCHLORIDE

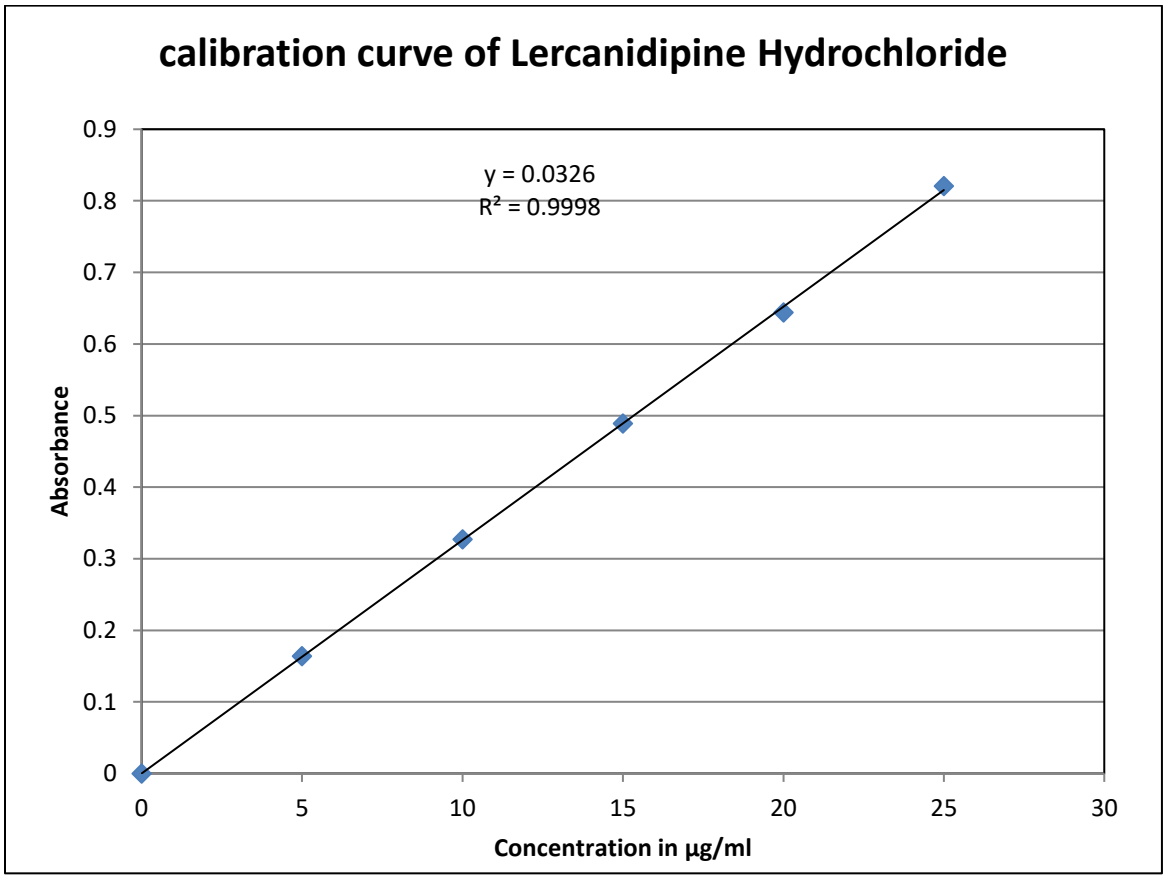
9.3.1.CALIBRATION CURVE OF LERCANIDIPINE HYDROCHLORIDE:

Measured the absorbance of the above prepared standard solutions at 238 nm. Plotted a graph of concentration (in μg/ml) on X axis and absorbance (in nm) on Y axis

TableNo: 11. Caliberation curve for Lercanidipine Hydrochloride

S. No.	Concentration (µg/ml)	Absorbance (nm)
1	0	0
2	5	0.178
3	10	0.336
4	15	0.489
5	20	0.644
6	25	0.807
Slope	**0.0326**	
R^2	**0.9998**	

Figure No: 8 : Caliberation Curve of Lercanidipine Hydrochloride



CHAPTER 10

FORMULATION

10. FORMULATION AND DEVELOPMENT OF LERCANIDIPINE HYDROCHLORIDE IMMEDIATE RELEASE TABLETS

Table. No: 12. FORMULATION F1-F8

INGREDIENTS(in mg)	FORMULATION BATCHES							
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
Lercanidipine Hydrochloride	10	10	10	10	10	10	10	10
Sodium Starch Glycolate (SSG)	3	6	9	12	-	-	-	-
Croscarmellose sodium (CCS)	-	-	-	-	3	6	9	12
Crospovidone / PVP	-	-	-	-	-	-	-	-
Starch 1500	-	-	-	-	-	-	-	-
Lactose	50	50	50	50	50	50	50	50
Mannitol	63	60	57	54	63	60	57	54
Magnesium Stearate	1	1	1	1	1	1	1	1
Sucralose	3	3	3	3	3	3	3	3
Average Weight	130	130	130	130	130	130	130	130

Table. No: 13. FORMULATION F9-F16

INGREDIENTS(in mg)	FORMULATION BATCHES							
	F9	F10	F11	F12	F13	F14	F15	F16
Lercanidipine Hydrochloride	10	10	10	10	10	10	10	10
Sodium Starch Glycolate (SSG)	-	-	-	-	-	-	-	-
Croscarmellose sodium (CCS)	-	-	-	-	-	-	-	-
Crospovidone / PVP	3	6	9	12	-	-	-	-
Starch 1500	-	-	-	-	3	6	9	12
Lactose	50	50	50	50	50	50	50	50
Mannitol	63	60	57	54	63	60	57	54
Magnesium Stearate	1	1	1	1	1	1	1	1
Sucralose	3	3	3	3	3	3	3	3
Average Weight	130	130	130	130	130	130	130	130

Procedure:

All the ingredients were weighed and mixed well. Then it is tableted by direct compression method - proton Mini Press

CHAPTER 11

EVALUATION

11. EVALUATION

11.1. PRE-COMPRESSION PARAMETERS:

A) Angle of repose:

Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane.

5 grams of the sample was taken in a funnel fixed in a holder (6 cm) above the surface at an appropriate height and a graph of sheet was placed below the funnel. The sample was passed through the funnel slowly. The height of the powder heap formed was measured. The circumference of the heap formed was drawn with a pencil on the graph paper. The radius was measured and the angle of repose was determined using the above formula. This was repeated five times for a sample.

Table. No: 14. Flow properties and corresponding Angle of Repose

Flow property	Angle of Repose (Degree)
Excellent	25-30
Good	31-35
Fair-aid not needed	36-40
Passable- may hang up	41-45
Poor- must agitate, vibrate	46-55
Very poor	56-65
Very, very poor	> 66

$$\theta = \tan^{-1} (h/r)$$

Where,

h = height,

r = radius,

θ = Angle of repose.

The results are given in results and discussion.

B) Determination of bulk density and tapped density:

A quantity of 5g of the powder (W) from each formula was introduced into a 25 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 sec intervals. The tapping was continued until no further change in volume was noted. The bulk density, and tapped density were calculated using the following formulas

$$\text{Bulk density}(\rho_b) = m / V_b$$

$$\text{Tapped density}(\rho_t) = m/V_t$$

Where,

m = mass of the powder,

V_b = initial or bulk volume,

V_t = final or tapped volume.

The results are shown in results and discussion.

C) Measurement of Hausner ratio and Carr's Index

a. Hausner's Ration:

Hausner's ratio indicates the flow properties of powder and measured by the ratio of tapped density to bulk density. Hausner's ratio was determined by the given formula:

$$\textbf{Hausner Ratio} = V_b/V_t$$

Where,

V_b = initial or bulk volume

V_t = final or tapped volume

The results are shown in results and discussion.

Table. No: 15. Scale of flowability

Compressibility index (%)	Flow character	Hausner Ratio
≤ 10	Excellent	1.10-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very poor	1.46-1.59
>38	Very, very poor	>1.60

b. Carr's Index/Compressibility Index:

Compressibility is the ability of powder to decrease in volume under pressure using bulk density and tapped density the percentage compressibility of powder were determined, which is given as carr's compressibility index. It is indirectly related to the relative flow rate. Carr's compressibility index was determined by the given formula

$$\text{\% Compressibility (Carr's index)} = \frac{\text{Tapped density - Initial bulk density}}{\text{Tapped density}} \times 100$$

The results shown in results and discussion.

11.2.EVALUATION OF LERCANIDIPINE HYDROCHLORIDE TABLETS:

a. Weight Variation Test:

The tablet of one particular batch should have uniformity in weight. If any weight variation is found, it should fall within the prescribed limits. According to USP maximum % deviation allowed are as follows :-

Table. No: 16.Weight Variation Test.

Average weight of tablets(mg)	Maximum % difference allowed
130mg or less	±10%
130-324mg	±7.5%
Above 324mg	±5%

A sample of 20 tablets is selected randomly from a particular batch and weighed individually and collectively. The average weight of the tablets is calculated. The individual weights are then compared with average weight. The weights of not more than two of the tablets should not differ and calculate the average weight by more than the prescribed limit and no tablet should differ by more than the double the limits.

$$\% \text{ Deviation} = \frac{\text{Tablet weight-Average weight}}{\text{Tablet weight}} \times 100$$

The results shown in results and discussion

b. Friability Test:

20 tablets were weighed and subjected to rotate on friability test apparatus. The drum rotated at a speed of 25 rpm for 4 minutes, then dedusted and reweighed the tablets. Percentage friability was calculated by the following formula.

$$\text{Percentage of Friability (\%F)} = 100\ (1 - w/w_0)$$

Where,

Wo = Initial weight,

W = Final weight.

Percentage friability of tablets less than 1% is considered acceptable. The results shown in results and discussion.

c. Hardness Test:

Hardness of a tablet determines its tensile strength. It must be such that the tablets withstand the shock of handling, packing, and shipping. It is measured in terms of load/pressure required to crush it when placed on its edge. Generally, two types of hardness testers are used to determine the hardness.

Monsanto Hardness Tester:

It consists of a barrel containing a compressible spring held between two plungers. The spring can be compressed by moving the knob forward. The tablet to be tested held between a fixed and moving plunger and reading of the indicator is adjusted to zero. The force applied to the edge of the tablet is gradually increased by moving the screw know forward until the breaks. The reading is noted from the scale which indicates the pressure required in kg or lb/$cm^2$to break the tablet. Hardness of 4kg/cm^2 is considered to be minimum requirement.

Pfizer Tablet Hardness Tester:

This is slightly improved instrument used for determing the hardness of tablet. It works on the principle of plier. Pressure gauze is fitted on one arm of the tester. The tablet to be tested is put vertically in between the jaws which are pressed with hand until the tablet breaks. The reading can be noted from the indicator of the pressure gauze in terms of kg or lbs.

The hardness of a sample batch of Escitaloparam tablets was carried out by using Monsanto type hardness tester. The hardness of the tablet kg / cm^2 was measured.

The results are shown in results and discussion.

d. Thickness Test:

Control of physical dimension of the tablets such as sizes and thickness is essential for consumer acceptance and to maintain tablet to tablet uniformity. Manufacturers set the limits on the thickness of the tablets of their products in order to avoid any problems during automatic

counting and packing. If the thickness of the tablet goes beyond a certain limit, it may block the channels of the machines. Hence there should be in-process control to maintain the thickness of the tablets. The dimensional specifications were measured using vernier calipers.

Six tablets from each batch were tested and average values were calculated.The thickness of the tablet is mostly related to the tablet hardness can be uses as initial control parameter.

The results are shown in results and discussion.

e. Diameter and Shape:

The diameter and shape of the tablets are determined by the dies and punches used for the compression. Less concave the punches, the more flat will be the tablets. Conversely, the more concave the punches, more convex would be the resulting tablets. Similarly, punches having raised impressions will produce recessed impressions on the tablets. Whereas punches having recessed impression, will produce raised impressions on the tablet surface. Therefore, proper selection of punches and dies should be done so as to produce tablets will desired diameter and shape.

f. Drug content:

Weigh and powdered 10 tablets in a mortar. From this powder equivalent to 100mg of Lercanidipine Hydrochloride was taken in a 100ml volumetric flask to this water was added and then the solution was subjected to sonication for about 10min's for complete solubilization of drug and the solution was made up to the mark with water filtered the drug content was estimated by measuring the absorbance at 244 nm by using UV-Visible spectrophotometer.

g. Disintegration Time:

The test is performed *invitro* to determine the time in which a tablet disintegrates in the water at the 37±2°C. The apparatus which is used to

simulate all the conditions of mouth, for the determination of disintegration time is called as Disintegration Time.

It consist of two hot plates with housing for beakers, thermostatically controlled heaters to maintain the temperature, two baskets each having provision for fixing 6 glass or plastic tubes provided with guided discs and stainless wire mesh. Each unit is suitable for performing two tests at a time.

The glass or plastic tubes are open at one end and fitted with sieve No. 10 mesh at the other end. The tubes are suspended in bath containing water or suitable liquid which is maintained through a distance of 75mm, the volume of the liquid and the distance of movement is adjusted in such a way that the highest point, the sieve should break the surface of the liquid.

six tablets are placed in each of the six tubes along with a guided plastic disc over the tablets tube and the assembly was suspended into the 1000ml beaker containing Water maintained at 37±2˚C and operated the apparatus for 15 minutes. The tubes are allowed to move up and down as per the specification discussed above and the disintegration time is noted when all the tablets particles have passed through the sieve. The disintegration time should comply with official time unless otherwise in the monographs. The assembly was removed from the liquid and the tablets were observed. If one or two tablets fail to disintegrate completely, repeat the test on 12 additional tablets. The requirement is met if not less than 16 of the total of 18 tablets tested are disintegrated.

h. Wetting time and water absorption ratio:

Wetting time of dosage form is related to with the contact angle. Lower wetting time implies a quicker disintegration of the tablet.

Wetting time:

It is closely related to the inner structure of the tablets and to the hydrophilicity of the excipients. To measure wetting time, five circular tissue papers of 10cm diameter are placed in a petridish with a 10cm

diameter. 10ml of water containing eosin, a water soluble dye, is added to petridish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as a wetting time.

Water absorption ratio:

A piece of tissue paper folded twice was placed in a small Petri dish containing 6 ml of water. A tablet was put on the paper & the time required for complete wetting was measured. The wetted tablet was then weighed. The water absorption ratio, *R* can be the determined according to the following equation;

$$R = 100 (Wa-Wb) / Wb$$

Where,

Wb; The weight of the tablet before keeping in the petridish.

Wa; The wetted tablet from the petridish is taken and reweighed.

i. Dissolution:

Dissolution Rate:

Dissolution rate is defined as the amount of solute dissolved in a given solvent per unit time under standard conditions of temperature, pH, solvent composition and constant solid surface area. The developed dissolution test can serve also a routine control mechanism to assure the proper dissolution characteristics, as well as the uniformity of regular production.

Measurement of the Intrinsic Dissolution Rate:

- This measurement is extremely important input factor during the initial drug screening and formulation development programs.
- Measurement over the entire physiological pH range can be very useful in predicting whether the absorption of moderately or poorly soluble drugs is dissolution rate limited.
- Such information is essential in order to develop a suitable dosage form that is free from bioavailability problems.

- The information also is very useful for improving existing formulations that have demonstrated bioavailability problems.
- It is important to point out while the intrinsic dissolution rate data is very useful in characterizing the solubility behavior of drug substance, it is of little value in describing the characteristics of the pharmaceutical forms.

Dissolution Apparatus of Immediate Release Lercanidipine Hydrochloride tablets:

invitro dissolution of Lercanidipine Hydrochloride was studied in USP dissolution apparatus (Electrolab) employing a Basket stirrer. 900 ml Water was used as dissolution medium at 50 rpm. The temperature of 37 ± 0.5 °C was maintained throughout the experiment. Complex equivalent to mg of Lercanidipine Hydrochloride was used in each test. 5 ml of sample of dissolution medium were withdrawn by means of syringe fitted with pre-filter at known intervals of time and analyzed for drug release by measuring the absorbance at 238 nm after suitable dilution with 6.8 pH phosphate buffer. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium. The amount of Lercanidipine Hydrochloride released was calculated and plotted against time and compared with marketed drug was studied.

Dissolution Study

***In-vitro* release profile:**

Medium : Water 900ml.
Apparatus : USP II (Paddle)
Speed : 50 rpm
Time : 30 minutes
Temperature : 37 ^{0}C ± 0.5 ^{0}C
λ Max : 238 nm

Perform the test on six tablets place one tablet in each dissolution vessel containing 900 ml of 6.8 pH Phosphate buffer maintained at 37 ^{0}C ± 0.5 ^{0}C. At specified time withdrawn required amount of sample and replace the same amount with (maintain sink condition), then absorbance was taken and calculate percentage release.

$$\% \text{ Purity} = \frac{\text{Absorbance X 900 X Dilution}}{\text{Slope X 1000 X label claim}} \times 100$$

The results are given in results & discussion.

j. Stability studies:

The optimized tablets were packed in amber-colored bottle, which was tightly plugged with cotton and capped. It was then stored at 40°C / 75% RH for 8 weeks. The tablets were evaluated for hardness, drug content and dissolution study and compared with tablets evaluated immediately after manufacturing.

CHAPTER 12

RESULTS AND DISCUSSION

12. RESULT AND DISCUSSION

12.1.Pre formulation Studies:

Organoleptic properties:

These tests were performed as per procedure. The results are illustrated in following table.

Table. No. 17: Organoleptic Properties

Test	Specification / limits	Observations
Color	White color	white powder
Odour	Odourless	Odourless

The result complies as per specification.

Angle of repose :

It was determined as per procedure given in material and method part. The results are,

Table. No.18: Flow properties

Material	Angle of repose
Lercanidipine Hydrochloride	$29^{o}.27"$

The result shows that drug having poor flow.

Bulk density and tapped density:

It was determined as per procedure given in material and method part. The results are,

Table. No.19: Density

Material	Bulk Density (gm/ml)	Tapped density (gm/ml)
Lercanidipine Hydrochloride	0.28	0.23

Powder compressibility:

It was determined as per procedure given in material and method part. The results are,

Table. No.20: Powder Compressibility

Material	Compressibility index	Hausner ratio
Lercanidipine Hydrochloride	18.92%	1.19

Melting point:

It was determined as per procedure given in material and method part. The results are,

Table. No. 21: Melting point

Material	Melting point range	Result
Lercanidipine Hydrochloride	185-188 °C	Complies

The result indicates that the Lercanidipine Hydrochloride drug was pure one.

SOLUTION PROPERTIES:

Solubility:

It was determined as per procedure given in 9.4.2 in material and method part. The following table 17 illustrated the result.

Table. No.22: Solubility

Test	Specification	Result
Solubility	water: 9.3 mg/100 ml ethanol 95%: 4.7 g/lOOml ethanol 99%: 4.7 g/lOOml dimethylformamide: >lo0 g/100 ml	Complies

The result complies as per specification.

Drug - Excipient Compatibility Studies

A) Physical Observation:

There are no such changes in the physical observation after mixing of ingredients.

B) Drug Identification by FTIR:

The graph is compared with the standard FTIR graph given in pharmacopoeia or prescribed standards and confirmed through the corresponding peaks.

PRECOMPRESSION PARAMETERS:

Table. No. 23: EVALUATIONS OF GRANULES

Batch NO.	Angle of Repose(^{0})	Bulk Density(g/ml)	Tapped bulk density(g/ml)	Carr's index (%)	Hausner's Ratio
F1	24°31'	0.518	0.622	14.33	1.13
F2	23°12'	0.533	0.634	13.28	1.12
F3	24°27'	0.540	0.628	14.76	1.14
F4	25°34'	0.521	0.626	13.24	1.16
F5	26°.52'	0.533	0.633	13.37	1.13
F6	25°.71'	0.541	0.631	12.59	1.12
F7	26°.69'	0.532	0.629	12.47	1.18
F8	26°.14'	0.538	0.630	11.43	1.17
F9	25°.33'	0.522	0.629	13.22	1.12
F10	26°.87'	0.524	0.636	13.71	1.11
F11	24°.32'	0.533	0.638	13.37	1.12
F12	25°.29'	0.538	0.634	13.22	1.12
F13	23°.09'	0.545	0.623	12.85	1.15
F14	24°.67'	0.539	0.625	13.26	1.14
F15	24°.31'	0.536	0.619	12.41	1.13
F16	24°.22'	0.537	0.612	12.49	1.14

Discussion:

The angle of repose for the formulated blend F1-F16 was found to be in the range 23^0.09' to 26^0.87' shows good flow property.

Compressibility index for the formulations F1-F16 found between 11.43% to 14.76% indicating the powder blend has the required flow property for compression.

Hausner's Ratio for the formulations F1-F16 found between 1.11 to 1.18 indicating the powder blend has the required flow property for compression.

EVALUATION OF LERCANIDIPINE HYDROCHLORIDE TABLETS:

Table. No: 24.WEIGHT VARIATION AND FRIABILITY:

Batch. No	Weight Variation (%)	Friability (%)
F1	130±1.22	0.61
F2	131±1.38	0.50
F3	129±1.34	0.59
F4	130±1.29	0.63
F5	130±1.41	0.55
F6	131±1.28	0.66
F7	132±1.26	0.51
F8	131±1.24	0.68
F9	129±1.46	0.69
F10	130±1.32	0.62
F11	129±1.26	0.51
F12	129±1.29	0.55
F13	131±1.02	0.64
F14	130±1.25	0.50
F15	131±1.24	0.63
F16	130±1.32	0.54

Discussion:

The weight variation of the tablet in the range of ± 1.02 % to ± 1.46 % (below 5%) complying with pharmacopoeial specification.

The friability of the tablet in the range of 0.50 % to 0.69% **(**below 1%) complying with pharmacopoeial specifications.

Table. No: 25. Thickness, Hardness and Disintegration Time:

Batch. No	Thickness (mm)	Hardness (Kg/cm^2)
F1	2.03±0.2	2.22
F2	2.01±0.2	2.33
F3	2.02±0.2	2.26
F4	2.03±0.2	2.23
F5	2.02±0.1	2.33
F6	2.03±0.3	2.25
F7	2.02±0.1	2.31
F8	2.02±0.2	2.26
F9	2.01±0.1	2.27
F10	2.02±0.2	2.25
F11	2.02±0.2	2.19
F12	2.01±0.3	2.24
F13	2.03±0.2	2.29
F14	2.02±0.3	2.33
F15	2.01±0.1	2.34
F16	2.02±0.2	2.27

Discussion:

The thickness of the formulations from F1- F16 was found to be in the range of 2.01±0.1 to 2.03±0.3 and hardness of the formulated tablets was found to 2.19 to 2.34 indicating a satisfactory mechanical strength.

Table. No: 26. Wetting Time and Disintegration Time:

Batch. No	Wetting Time (Sec)	DISINTEGRATION TIME (seconds)
F1	90	110
F2	85	102
F3	73	93
F4	69	85
F5	103	160
F6	98	138
F7	83	115
F8	73	105
F9	32	63
F10	29	55
F11	25	42
F12	19	35
F13	178	223
F14	154	201
F15	133	192
F16	111	150

Discussion:

The Wetting time of the formulations from F1- F16 was found to be in the range of 19-178 seconds. Lower wetting time implies a quicker disintegration of the tablet. F12 shows very lower wetting time it reflects in faster DT.

Water absorption ration is around 67% shows for the formulation F8.

Table. No:27. Cumulative % Release of Lercanidipine Hydrochloride Mouth Dissolving Tablets F1-F4

Time (mts)	% Drug Release of Formulations			
	F1	F2	F3	F4
0	0	0	0	0
1	31.03	36.34	39.22	41.13
2	43.47	51.07	54.61	56.22
4	49.04	65.18	69.13	70.11
6	58.75	72.18	75.96	79.74
8	66.21	89.72	86.27	88.33
10	73.66	94.27	97.43	96.24
12	88.20	99.42	99.26	99.31
15	98.45	---	---	---
17	---	---	---	---

Fig. No:15. Cumulative % Release of Lercanidipine Hydrochloride Mouth Dissolving Tablets F1-F4

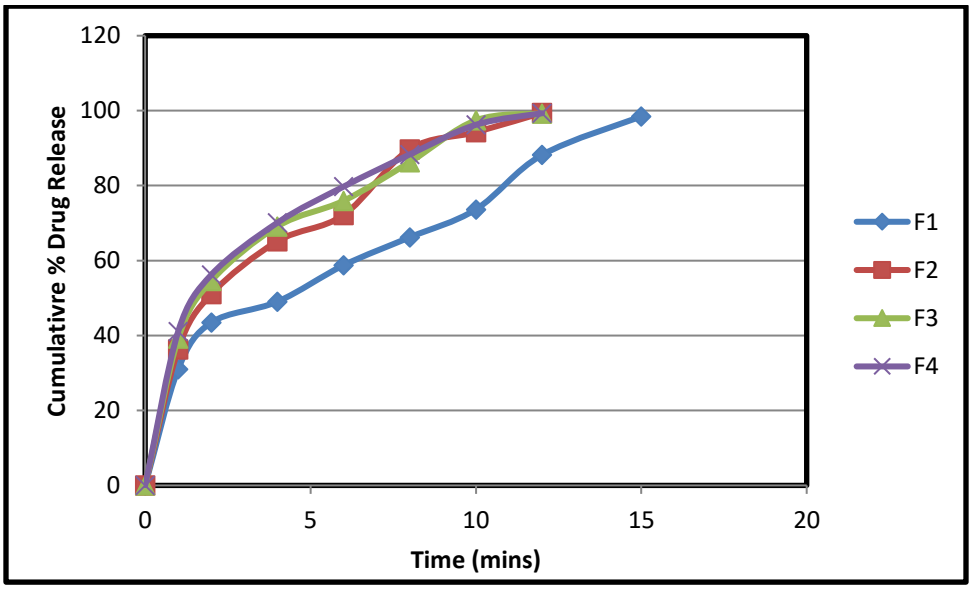


Table. No:28. Cumulative % Release of Lercanidipine Hydrochloride Mouth Dissolving Tablets F5-F8

Time (mts)	% Drug Release of Formulations			
	F5	F6	F7	F8
0	0	0	0	0
1	35.47	39.67	43.82	44.34
2	44.22	46.18	56.21	60.07
4	56.03	59.72	63.49	72.18
6	63.97	68.23	71.02	80.40
8	71.08	73.70	79.08	89.72
10	79.94	83.46	87.53	94.27
12	86.28	90.24	93.15	99.42
15	91.62	98.38	99.87	---
17	97.21	---	---	---

Fig. No:16. Cumulative % Release of Lercanidipine Hydrochloride Mouth Dissolving Tablets F5-F8

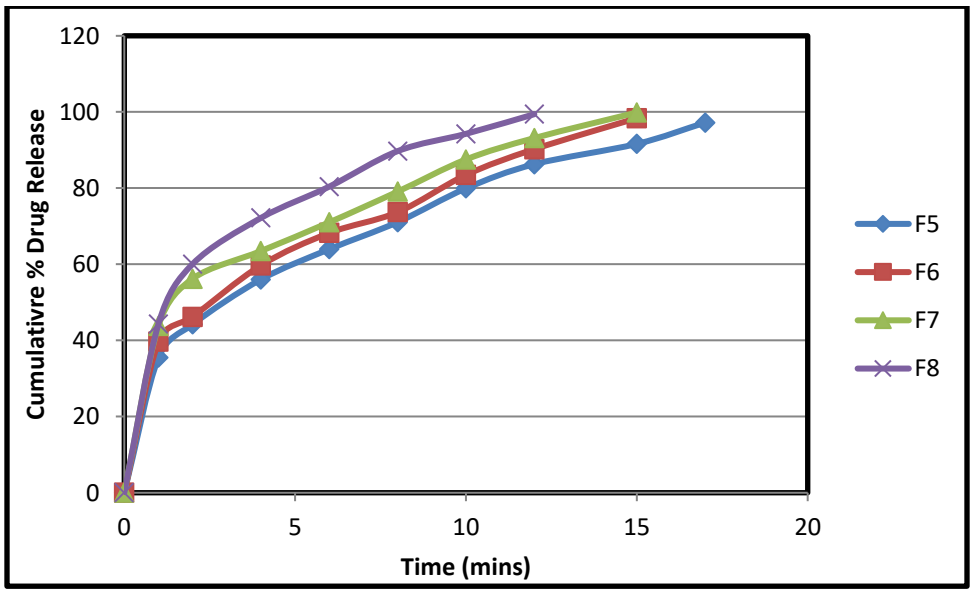


Table. No:29. Cumulative % Release of Lercanidipine Hydrochloride Mouth Dissolving Tablets F9-F12

Time (mts)	% Drug Release of Formulations			
	F9	F10	F11	F12
0	0	0	0	0
1	33.43	34.61	36.23	41.81
2	45.96	49.14	51.78	59.76
4	53.07	62.49	68.45	72.33
6	64.23	71.93	79.17	85.87
8	76.88	83.74	87.92	99.22
10	89.26	92.57	97.48	---
12	98.75	99.22	---	---
15	---	---	---	---
17	---	---	---	---

Fig. No:17. Cumulative % Release of Lercanidipine Hydrochloride Mouth Dissolving Tablets F9-F12

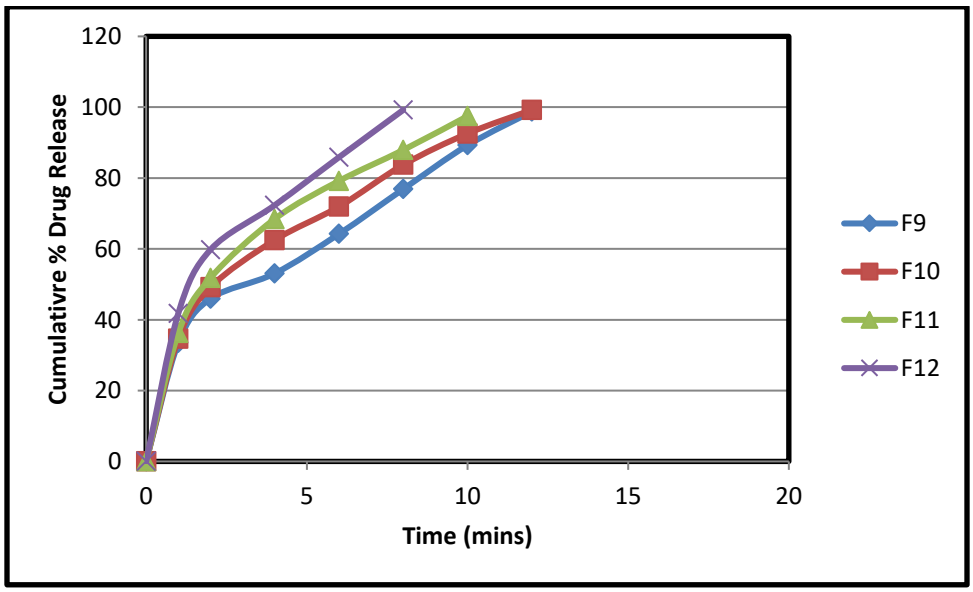


Table.No.30: Cumulative % Release of Lercanidipine Hydrochloride Mouth Dissolving Tablets F13-F16

Time (mts)	% Drug Release of Formulations			
	F13	F14	F15	F16
0	0	0	0	0
1	12.29	19.74	21.35	24.21
2	19.71	27.24	39.74	40.39
4	29.37	36.42	44.64	53.91
6	34.92	41.37	52.47	66.26
8	41.24	51.79	61.88	75.54
10	49.33	60.28	70.22	89.19
12	58.76	69.96	76.34	93.65
15	65.22	74.44	83.14	96.78
17	71.24	80.94	89.47	98.37

Fig.No.18: Cumulative % Release of Lercanidipine Hydrochloride Mouth Dissolving Tablets F13-F16

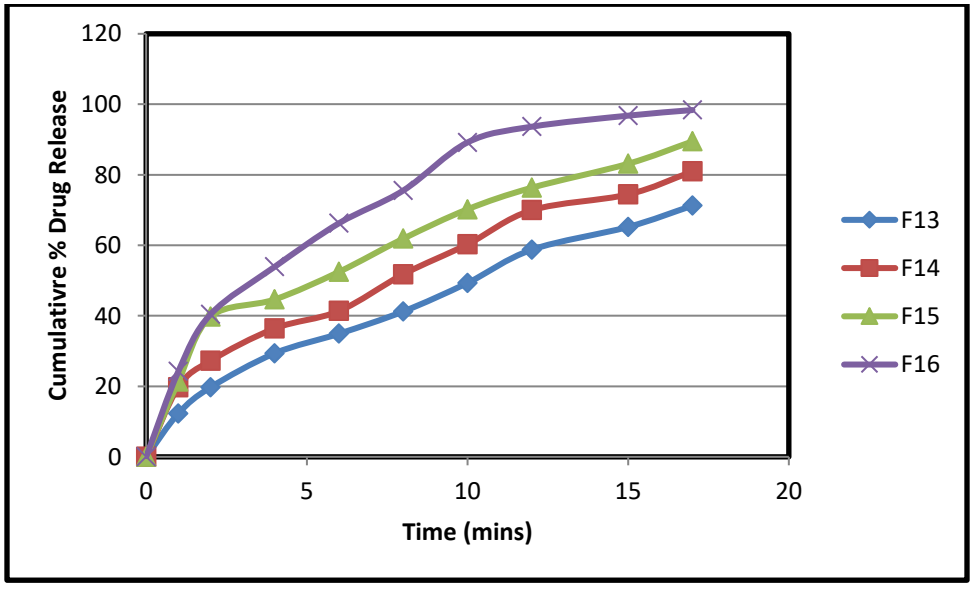
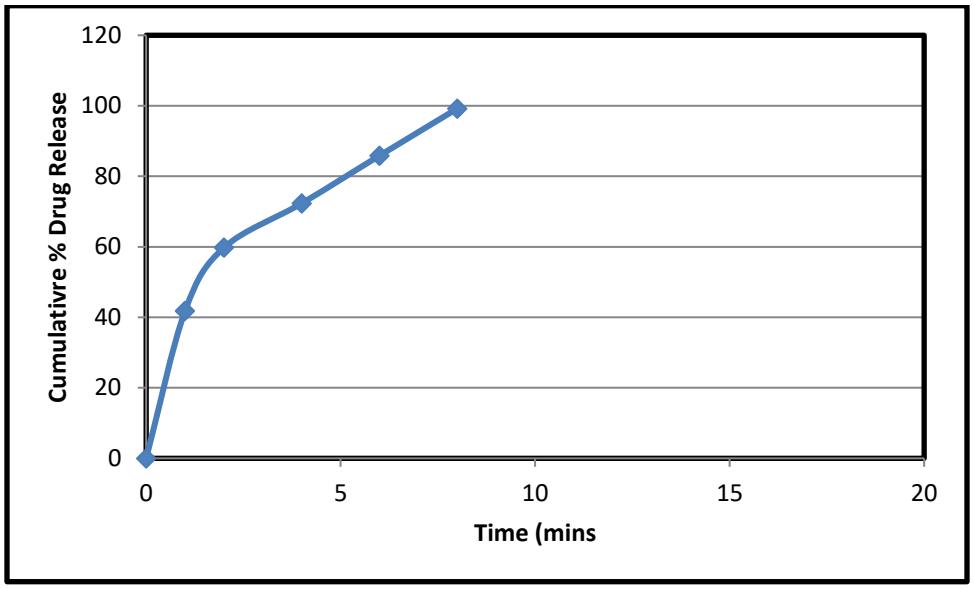


Fig.No.31: Graph: Cumulative % Release of Lercanidipine Hydrochloride Mouth Dissolving Tablets F12



8.9 STABILITY STUDIES:

Table no. 26: Stability studies of optimized formulation F12

Time (days)	25°C ± 2°C/60% RH ± 5% RH, 30°C ± 2°C/65% RH ± 5% RH, 40°C ± 2°C/75% RH ± 5% RH			
	Hardness(kg/cm²)	Drug content (%)	% Drug release	DT
30	2.23	99.11	99.29	36
60	2.22	99.03	99.12	37

- Stability studies were carried out on selected formulations (F12) as per ICH guidelines. There was not much variation in matrix integrity of the tablets at all the temperature conditions. There was no significant changes in drug content, physical stability, hardness, friability, drug release, for the selected formulation F12 after 90 days at 25°C± 2°C / 60% ± 5% RH, 30°C ± 2°C / 65% ±5% RH and 40°C ± 2° / 75% ± 5% RH.

CHAPTER 13

SUMMARY AND CONCLUSION

13. SUMMARY AND CONCLUSION

The present study involves formulation and evaluation of immediate release tablets of Lercandipine Hydrochloride. Endeavours with respect to Direct compression method used for formulating tablets was best suitable to achieve 100% results.

Preformulation studies involving organoleptic bulk density, angle of repose, tapped density, compressibility index, hausner ratio, melting point range, pH and solubility were carried out as per USP specifications.

Polymers such as CrosPovidone, Croscarmellose Sodium (CCS), Sodium Starch Glycolate (SSG), Starch 1500 were utilized in the trails. All the physical evaluations carried in preformulation studies were carried out on all the four different polymers utilized. All the formulations exhibited values within the acceptable range.

Tablets were evaluated for weight variations, hardness, friability, thickness and Dissolution studies.

Release studies were carried out in Phosphate buffer, for 30 minutes. Evaluated samples for all the three polymer systems. Results indicated that formulation F12, gave 99.14% release within 8 minutes which is formulated with CrosPovidone alone. Assay was carried out for formulation F12 and was found to be 99.42%.

Remaining formulations gave fluctuating release profiles. The formulation F12 was considered to be better among the trails accomplished.

CHAPER 14

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